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OF

# INTERNAL MEDICINE

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## CYSTIC DISEASE OF THE LUNG

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NEW YORK

Air cysts of the lung which produce symptoms sufficient to call clinical attention to their existence must be considered an uncommon condition. Croswell and King<sup>1</sup> have been able to find reports of only 121 cases, including the 108 case reports compiled by Koontz.<sup>2</sup> The fact is, however, that although rarely encountered clinically, cystic disease of the lung not infrequently presents important diagnostic and therapeutic problems. A report, together with a discussion of a group of cases illustrating the clinical features as well as the diagnostic and therapeutic problems which they presented, is therefore warranted.

Most of the publications on the subject have been essentially from the standpoint of the pathology and pathogenesis. In occasional instances case reports have been published dealing with the results of treatment. This paper aims to illustrate some important types of cystic disease of the lung, especially from the point of view of clinical manifestations, diagnostic features and therapeutic approach. In addition, the mechanism underlying the physical signs and symptoms will receive special consideration because it sheds a good deal of light on the general subject of pneumodynamics.

### REPORT OF CASES

CASE 1—A man aged 46 was admitted to the Mount Sinai Hospital on June 27, 1933, because of the occurrence of moderately profuse fresh hemoptyses for ten days. There was little or no associated cough, and no constitutional symptoms were manifest.

The patient stated that on six different occasions during the previous twenty-nine years he had experienced similar episodes of hemoptysis at varying intervals and of variable severity. On each occasion the cough and constitutional symptoms were minimal, and recovery was complete. During the intervening periods he was free from all symptoms of pulmonary involvement.

General physical examination, as well as an examination of the upper respiratory tract and lungs, showed no abnormalities to account for the hemoptysis. All the ordinary laboratory tests gave negative results.

Roentgen examination of the lungs (fig 1 left) revealed a number of circular and oval cavities in the lower half of each lung which had the appearance

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From the Thoracic Group of the Mount Sinai Hospital

1 Croswell, C V, and King, J C. Congenital Air Cyst of the Lung. Report of Case, J A M A **101** 832 (Sept 9) 1933.

2 Koontz, A R. Congenital Cysts of the Lung. Bull Johns Hopkins Hosp **37** 340 (Nov) 1925.

of air cysts. The largest of the cavities, which was situated laterally in the lower lobe of the right lung, was about  $2\frac{1}{2}$  inches (6.5 cm) in diameter and nearly full of fluid.

The hemoptysis ceased shortly after the patient's admission to the hospital, and after a few days he was discharged free from symptoms.

*Comment*—In this case hemoptysis was the only manifestation of the condition on seven different occasions over a period of twenty-nine years. It is to be noted that there was no antecedent history of inflammatory pulmonary disease and that there was no evidence in the roentgenogram of inflammatory changes in the pulmonary parenchyma. These facts, as well as the bilateral distribution of the air cysts, suggest a congenital origin of the condition.

Whether the bleeding had its origin in one of the air cysts and its spontaneous arrest was due to compression of the bleeding vessel when

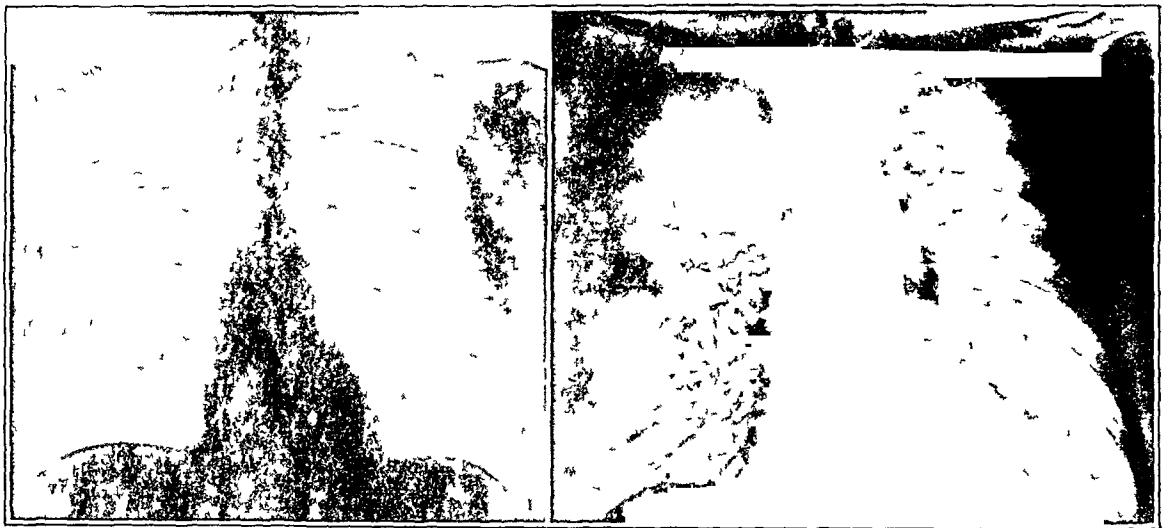


Fig 1 (case 1)—The figure on the left is a roentgenogram showing a number of circular and oval air cysts in the lower lobe of each lung. The large cyst situated laterally in the lower lobe of the right lung is nearly full of liquid. On the right is a bronchogram in which some of the air cysts are outlined by iodized poppy-seed oil.

the cyst was filled with blood could only be conjectured. It was the blood-filled cyst that was obviously responsible for the dense, round shadow seen in figure 1, and its spontaneous evacuation through the bronchi was demonstrated in the roentgenogram made three days later. The existence of a free bronchial communication with the air cyst in question could have been inferred from the foregoing consideration, and it was demonstrated when iodized poppy-seed oil 40 per cent which was introduced through the trachea, found its way readily into that cyst (fig 1, right).

Some of the cysts were not outlined, but that did not exclude the existence of a bronchial communication, as the failure of the iodized

poppy-seed oil to penetrate those cysts may have been due to the tortuosity of the bronchial tract. It is probable that some communication with a bronchus is always present, otherwise the air within a cyst would absorb, and it would collapse. The size of a cyst and the changes which it may show from time to time depend on the character of the bronchial communication. A cyst will remain the same size or will enlarge very slowly if its bronchial communication acts as a two way valve, it will rapidly increase in size, and the intracystic pressure will rise (even to the point of rupture) if the bronchial communication acts as a check-valve. On the other hand, a cyst will collapse if its bronchial communication is shut off and if its air content is gradually absorbed.

From a therapeutic point of view pneumothorax was considered in this case as a method for the control of bleeding from the cyst. The introduction of air into the general pleural cavity, by producing pulmonary relaxation, might result in complete occlusion of the already tortuous tract of communication between the cyst and the bronchial tree. That would lead to the obliteration of the cyst through the absorption of its air content once the source of its continued renewal (open bronchial communication) was abolished. In other words, the induced pneumothorax need not be under high pressure to accomplish the desired effect. Relaxation pneumothorax will, therefore, be tried if hemoptysis recurs. The presence of multiple cysts, as well as the bilaterality of the process, precludes more radical therapeutic procedures, such as surgical extirpation.

This patient has been under observation since his discharge from the hospital. There has been no recurrence of hemoptysis. He has remained in normal health, and the pulmonary status has not shown any change.

CASE 2—A married woman aged 23 was admitted to the Mount Sinai Hospital on June 15, 1931, having been referred for study because of an obscure pulmonary condition. In 1926 she was confined to a hospital in another city because of signs and symptoms suggestive of a "peculiar" pneumonia, from which she made a complete recovery after about two weeks. She remained well until August 1929, when, three days post partum, she suddenly experienced severe pain in the right side of the chest, associated with moderate dyspnea. There was no cough or fever, and the pain as well as the dyspnea disappeared within twenty-four hours.

The roentgenogram at that time was interpreted as showing spontaneous tension pneumothorax of the right side, probably of tuberculous origin. Though free from symptoms, the patient took a "cure" for ten months, at the end of which period she had gained considerable weight.

For one year previous to admission to the Mount Sinai Hospital the patient felt well except for infrequent episodes of pain in the right side of the chest and dyspnea.

On admission the patient appeared to be in good health, and a general physical examination did not reveal any abnormality. Examination of the chest showed hyperresonance and diminished to absent breathing over the entire right lung as



well as moderate displacement of the heart and mediastinal structures to the left. The left lung did not show any abnormalities. The signs were suggestive either of a tension pneumothorax or of obstructive emphysema of the right lung. In the absence of a history of aspiration of a foreign body or other signs and symptoms of bronchostenosis with a ball-valve type of occlusion, the presence of a tension pneumothorax was considered as more likely. However, bronchoscopic examination would have been necessary in order to establish the differential diagnosis with absolute certainty.

At that point roentgen examination proved most helpful (fig 2) by showing the presence of an air space in the apex of the right lung, extending to the level of the third rib anteriorly. Below that there were numerous air cysts, some of

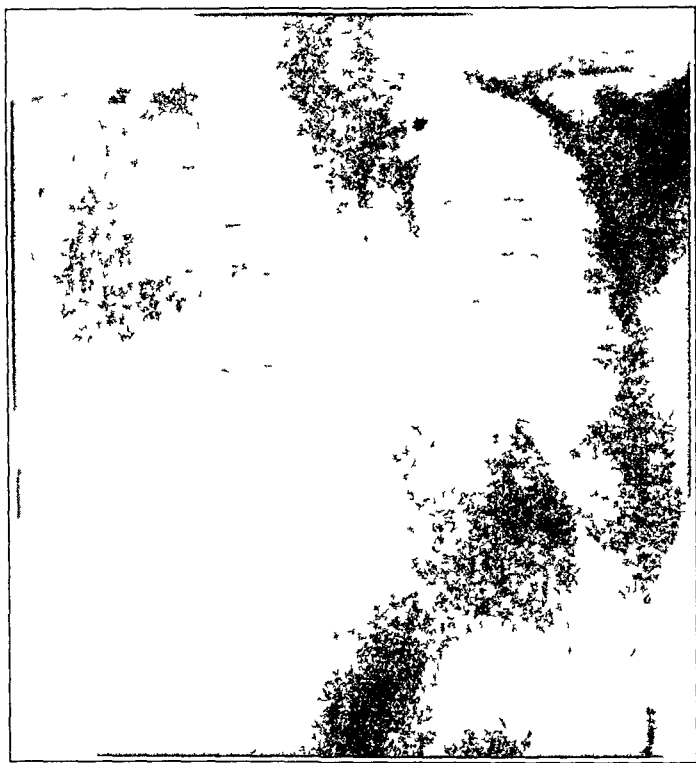


Fig 2 (case 2) —Roentgenogram showing a large air space (pneumothorax) in the apex of the right lung. Below this there are numerous air cysts. Note the displacement of the heart and mediastinum to the left.

which were several inches in diameter. The right lung extended beyond the midline and displaced the heart and mediastinum to the left. The pleura was thickened over the greater part of the right lung.

A bronchogram showed a displacement of the trachea and of the right main bronchus into the left side of the chest. On the right side only the main branches were outlined. On the left side there was some distortion of the bronchial tree due to the displacement.

Roentgenoscopy disclosed an interesting phenomenon. Since on deep inspiration the air cysts in the right lung were seen to expand and indent the air space in the apical field, there was thought to be an area of pneumothorax rather than a large air cyst in the apex.

One week after admission to the hospital, following an attack of sneezing the patient experienced a sudden severe pain in the right side of the chest which lasted for a few hours, though the acute phase subsided in a few moments.

The patient was discharged from the hospital eleven days after admission and since then has been under observation for nearly three years. She has continued in normal health except for episodes of mild pain in the right side of the chest, which she has learned to regard with little concern. The pulmonary status has remained unchanged.

*Comment*—In this instance of multiple cysts of the right lung there apparently were no symptoms for many years. After 1929 recurring episodes of pain in the chest and dyspnea were the only manifestations. A congenital basis may be assumed in this case because there was no suggestive history prior to 1929, at which time the lesion was known to be fully developed.

The case presented a number of interesting problems. The exact nature of the large air space in the apex of the right lung had to be determined. In the roentgenogram that space looked different from the other air spaces, which were obviously air cysts. Its appearance suggested a localized pneumothorax, and that impression was strengthened by roentgenoscopic evidence, which showed that on deep inspiration the surrounding air cysts indented that air space. The presence of a tension pneumothorax was at first suspected, and it was thought that it might be responsible in part for the displacement of the mediastinum to the left. A manometric reading of the air pressure within the space was therefore taken (an ordinary pneumothorax apparatus being used) and there was found to be a negative pressure of from 8 to 2 cm. of water. The finding of such a high negative pressure confirmed the impression that the air space was a localized pneumothorax, for the air pressure in a pulmonary cyst is either atmospheric or higher and never markedly negative. Since this localized pneumothorax was not under tension, it could not account, even in part, for the marked mediastinal displacement.

The probable mechanism operative in this case was conceived as follows. The displacement of the mediastinum to the left was due to the pressure exerted by numerous distended air cysts in the right lung with an atmospheric or positive intracystic pressure. The positive pressure in some of the air cysts was due to their tortuous bronchial communications, which acted like check-valves. The localized pneumothorax in the apex of the right lung was apparently due to the spontaneous rupture of one of the cysts when its intracystic pressure became relatively too high for the strength of its wall in the presence of a relatively low intrapleural pressure outside the cyst wall. The pneumothorax remained localized because of existing pleural adhesions.

The pneumothorax was chronic and persistent because of the following mechanism. Immediately after the rupture of a cyst the pneumothorax was under considerable pressure (atmospheric or higher), thus sealing off the opening caused by the rupture of the cyst. In the course of time the air in the pneumothorax space was gradually absorbed, with a corresponding fall in pressure. Because of the decreasing intrapleural pressure in the localized pneumothorax, there eventually resulted another spontaneous rupture of the weaker adjacent air cysts, with a renewal of the pneumothorax and repetition of the entire cycle, namely, a recurrent pneumothorax incidental to recurrent rupture of adjacent air cysts.

The associated episodes of pain in the chest and dyspnea depended on the size of the ruptured cyst and the tension of the resulting pneumothorax, hence the varying severity of the symptoms.

From a therapeutic point of view it seemed desirable at first to attempt the further obliteration of the pleural space by injecting irritating fluids and thus preventing the recurrence of the acute episodes of symptoms. However, further consideration led to the conclusion that either the patient had become accustomed to these episodes or the tissues had become insensitive, with the result that the symptoms had become too insignificant to warrant the instituting of any therapeutic procedure which entailed a risk.

The feasibility of the injection treatment of cysts of the lung was demonstrated in the case of a child reported by Groswell and King.<sup>1</sup> They injected iodized poppy-seed oil into the cavity of a huge balloon cyst of the lung. That was followed by a severe inflammatory reaction, with formation of pus which required aspiration. The reaction subsided after a short time and was followed by rapid disappearance of the cyst, with resulting clinical cure of a condition which had previously appeared to be distressing and hopeless.

It is worth mentioning that the logical evaluation of the nature and prognosis of the condition in the present case has made it possible to advise the patient to continue to lead a normal life, without undue restriction, despite the existence of striking changes in the intrathoracic organs.

CASE 3—A married man aged 46 was admitted to the Mount Sinai Hospital on Feb. 13, 1931, with a history of moderately productive cough for five years not associated with constitutional symptoms. Three months before admission he had a hemoptysis of about 8 ounces (240 cc.) of bright red unclotted blood, followed by expectoration of blood during the subsequent three weeks. The sputum was reported to have contained tubercle bacilli on one occasion. Because of the diagnosis of pulmonary tuberculosis the patient was sent to a sanatorium, where he remained for three months. The observations made at the physical and roentgen examination of the lungs and the uneventful general course were

not typical of clinical pulmonary tuberculosis. Repeated examination of the sputum did not show any tubercle bacilli. The patient was therefore referred to the Mount Sinai Hospital for study and treatment.

On admission the patient's complaints were limited to a slight productive cough and moderate dyspnea on exertion. The results of physical examination of the lungs were inconclusive and merely suggested the presence of moderate fibroid changes in the right lung.

Roentgen examination showed a diffuse fibrotic process involving both lungs, with thickening of the pleura and diaphragmatic adhesions which were not characteristic of tuberculosis. In addition, there was a dense shadow at the root of the right lung extending outward beyond the parasternal line from the level of the fourth to the seventh rib anteriorly. The nature of the shadow could not be definitely determined from its roentgenographic appearance. It was suggestive either of infiltration or of new growth.

Bronchoscopy revealed a crescentic fold running from the lower lip of the right bronchus into the mesial and posterior walls, giving the appearance either of a congenital anomaly or of a healed granulomatous lesion. Specimens taken at various bronchoscopic examinations were reported by the pathologist at one time as cartilage and atrophic mucosa, at another time as showing evidence of nonspecific inflammation and at a later time as showing cells suspiciously like tumor cells.

Bronchography with the aid of iodized poppy-seed oil was not satisfactory. The lateral view showed the bronchi somewhat distorted and pushed posteriorly. The sputum was examined repeatedly, but no tubercle bacilli were observed. The Wassermann reaction of the blood was four plus.

As the bronchial and pulmonary picture could possibly have been due to syphilis, rare as such a condition may be, appropriate therapy was instituted. Under antisyphilitic treatment the patient's condition improved generally, but the roentgenographic appearance of the lungs remained unchanged. The patient left the hospital and was to be followed in the clinic.

A few weeks after his discharge the cough and expectoration became more pronounced. Simultaneously, wheezing was noted, which was suggestive of stenosis of the bronchi of the right lung. Because of the changes in the patient's condition and also because of a suspicion of the presence of tumor cells in the specimen removed during the last bronchoscopic examination, he was readmitted to the hospital on April 30, 1931, for bronchoscopic reexamination. Bronchoscopy was performed in the usual manner. After it was completed, uneventfully, the patient sat up and coughed. Almost immediately thereafter he became unconscious, and the characteristic signs and symptoms of a cerebral lesion, including such manifestations as profound coma, changes in the reflexes, rigidity and convulsive seizure, promptly developed. He died about twelve hours later.

The postmortem examination showed that the right lung was voluminous, owing to the presence of a number of very large, thin-walled air cysts situated mainly subpleurally. The cysts were present in all three lobes, but the middle lobe appeared to be particularly involved. The upper lobe was curiously distorted, having been twisted forward, upward and medially so that it was situated in front of the trachea in the anterior mediastinum. This displacement was due primarily to the pressure of the air cysts in the lateral portion of the upper lobe and to the marked ballooning of the middle lobe, which was almost completely converted into a cystic mass the size of a large grapefruit. Corresponding to the dense hilar shadow seen in the roentgenogram, there was a firm mass, which on section proved to be a large blood clot, in one of the cysts in the upper lobe of the right

lung The lower lobe showed fewer and smaller air cysts The pulmonary parenchyma of the right lung showed diffuse and marked fibrosis throughout, leaving little alveolar tissue intact Widespread pleural adhesions bound the lung firmly to all the surrounding structures

The bronchi of the right lung presented a distorted appearance The main bronchus was twisted somewhat irregularly, resulting in a good deal of narrowing The branch to the middle lobe was directed forward and somewhat upward from its origin so that the normal ridge formed by the origin of the branch to the lower lobe was greatly accentuated and distorted and gave the appearance of a thick crescentic fold which largely occluded its orifice and which corresponded to the bronchoscopic appearance previously described

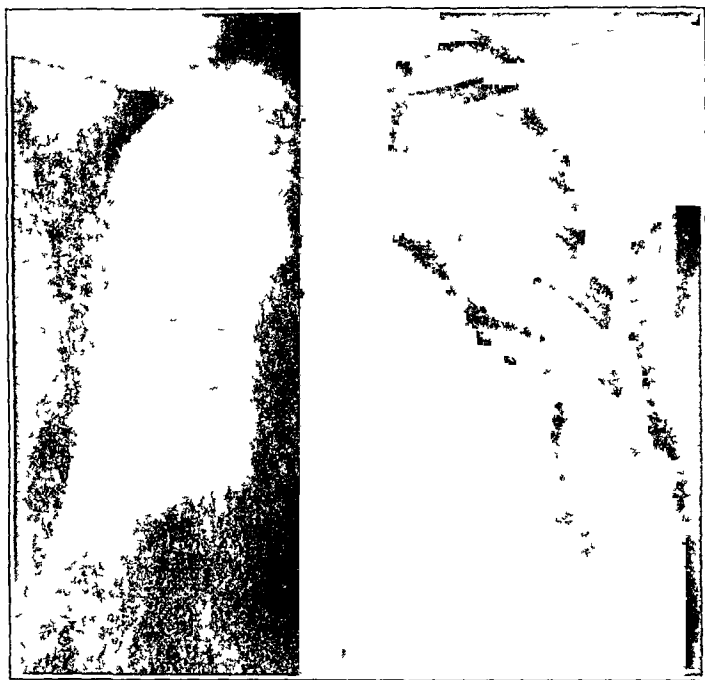


Fig 3 (case 4) —Roentgenogram showing small shadows scattered throughout both lungs which are suggestive either of "healed" miliary tuberculosis or of pulmonary vascular disease with fibrosis In the lower lobe of the right lung a large bullous cyst is seen adjacent to an area of marked pulmonary fibrosis

The left lung also showed extensive fibrosis and pleural adhesions as well as evidence of widespread alveolar emphysema, with a tendency to bullous formation

The other important change observed was syphilitic mesaortitis No evidence of bronchoscopic damage was revealed The autopsy did not include the brain

CASE 4—A man aged 65 was admitted to the Mount Sinai Hospital on Dec 10, 1932, because of three episodes of hemoptysis during the preceding three weeks Until about eight months before admission he considered himself in normal health During the subsequent eight months he experienced some weakness, a loss of 30 pounds (13.6 Kg) in weight, pains in the upper part of the right side of the chest and finally the three episodes of moderate hemoptysis

On admission the patient appeared to be in fairly good health and coughed only moderately The temperature was normal

Physical examination revealed moderate general cardiac enlargement of the hypertensive type. The blood pressure was 220 systolic and 130 diastolic. However, there were practically no signs or symptoms of cardiac decompensation. The significant pulmonary findings included diminished breathing and fine moist râles over the lower lobe of the right lung.

The Wassermann reaction of the blood was negative. Repeated examination of the sputum did not show any tubercle bacilli.

Bronchoscopic examinations did not disclose any obvious cause for the recurring hemoptysis.

The roentgenogram (fig 3) showed a diffuse fibrotic process throughout both lungs, with the exception of the lower lobe of the right lung, where the appearance was that of bullous emphysema. Whether the process in the lungs



Fig 4 (case 5) —Roentgenogram showing a large air cyst in the apical portion of the right lung adjacent to an area of fibrosis. The bronchi in the upper lobe are incompletely outlined and are apparently distorted by the air cyst.

was of tuberculous origin or was due to pulmonary vascular disease was not apparent. The association of diffuse pulmonary fibrosis with the bullous type of cystic disease of the lung was well illustrated in this case.

The patient left the hospital after a short, uneventful stay but continued under observation in the clinic. One year later the hemoptysis recurred, but the pulmonary status remained unchanged.

**CASE 5**—A man aged 60 was admitted to the hematologic clinic of the Mount Sinai Hospital on May 28, 1934, with signs and symptoms suggestive of polycythaemia vera. In Dr Nathan Rosenthal's opinion the blood picture (hemoglobin, 111 per cent, erythrocytes, 8,250,000, leukocytes, 24,000, and platelets, 1,500,000) as well as the clinical picture were typical of polycythaemia vera. The patient presented no pulmonary symptoms either on admission or at any previous time. However, routine roentgen examination of the lungs disclosed a large air cyst in the apical portion of the right lung adjacent to an area of fibrosis (fig 4).

*Comment*—In case 3 the diagnosis of cystic disease of the lung was not made ante mortem. On the one hand, there were two or three possible causes for the hemoptysis and the pulmonary changes as revealed by various studies, namely, tuberculosis, syphilis and possibly bronchopulmonary neoplasm. On the other hand, nothing was disclosed by the studies to suggest cystic disease of the lung. In cases 4 and 5 the diagnosis was easily made on a clinical basis.

In all three cases cystic disease of the lung was associated with a widespread fibrotic process in the affected lung. The cause of the widespread fibrosis was not apparent. Whatever the etiology of the pleuropulmonary fibrosis, it in turn was undoubtedly responsible for the cystic changes which developed to such a marked degree in case 3 and to a lesser extent in the other two cases. In this connection the pathologic changes in the left lung in case 3 (fibrosis, alveolar emphysema and scattered bullous formation) were most interesting, suggesting an earlier phase in the evolution of a pathologic process similar to the one in the right lung.

As is well known, emphysema results from causes which weaken the normal resistance of the pulmonary parenchyma. It is seen, for instance, in the neighborhood of areas of consolidation or fibrosis in cases of pyogenic or tuberculous bronchopneumonia, where areas of infiltration or fibrosis are usually surrounded by a ring of emphysematous vesicles (so-called compensatory emphysema). At the apex of the lung, along the anterior margins and at the base or in other regions where the pulmonary tissue is poorly supported the emphysema is likely to assume the form of large bullae.

In all these instances there is destruction of alveolar tissue. As a result the adjacent alveoli and alveolar passages are deprived of their former elastic support. Lacking that support, the intra-alveolar pressure causes distention which is progressive and may result in the formation of blebs or bullae of greater or smaller size, depending on the special conditions which prevail locally. The greater the destruction of pulmonary parenchyma, the greater will be the tendency to emphysema and the formation of air cysts.

In case 3 the mechanism of the subsequent changes in the right lung and bronchi was not difficult to recognize. As the air cysts developed and then bronchial communication became more and more tortuous they grew in size, and the intracystic pressure increased by the mechanism previously elucidated (comment on case 1). The pressure of the enlarging, tense cysts was responsible for the marked distortion of the bronchi. Rupture of the cysts, with resulting spontaneous pneumothorax, was precluded in that instance by the widespread pleural obliteration.

The association of the pulmonary changes with the existing polycythemia in case 5 may be purely accidental. It is conceivable, however, that the two conditions may be etiologically related. On the one hand, pulmonary fibrosis, if extensive enough, may lead to secondary polycythemia as well as to the formation of air cysts; on the other hand, pulmonary vascular engorgement or thromboses incidental to polycythemia may lead to pulmonary fibrosis and, secondarily, to the formation of air cysts. One can merely speculate on this phase of the subject until a larger material is available for study.

CASE 6—A man aged 45 was admitted to the Mount Sinai Hospital on Jan 26, 1932, because of productive cough of many years' duration. For four months before admission the cough and expectoration had become more severe, the expectoration amounting to about 4 or 5 ounces (120 or 150 cc) in twenty-four hours. There were no associated constitutional symptoms, and the sputum never had a foul odor.

On admission there were dullness and harsh almost bronchial breathing over the mesial half of the lower lobe of the left lung. The roentgenogram showed bullous emphysema in the lateral portion of the lower lobe. In addition, there was evidence of a chronic pneumonic process as well as of diaphragmatic and pleuropericardial adhesions at the base of the lung.

Bronchoscopy of the left lung revealed that the bronchi were straighter and closer to the median line than normally. Several small elevations were noted over the cartilaginous rings, suggesting kinking of the bronchi due to outside pressure. The bronchi of the lower lobe were dilated, and a small amount of pus was found in them. Injection of iodized poppy-seed oil through the chest wall into one of the blebs, under fluoroscopic control, showed the oil spreading over the emphysematous blebs and entering the dilated bronchi in the lower lobe, thus confirming the diagnosis of cystic disease associated with bronchiectasis in the lower lobe of the left lung.

CASE 7—A man aged 53 was admitted to the Mount Sinai Hospital on Dec 14, 1931, for observation because of a history suggesting the presence of a pulmonary abscess.

The patient stated that for many years he had been subject to frequent "colds" with productive cough of short duration. For about seven months before admission, following a "cold," the cough and expectoration continued to increase, the expectoration amounting to 4 ounces (120 cc) in twenty-four hours. Five months later the sputum had a foul odor for a period of two weeks. Shortly thereafter the sputum was blood-tinged. Night sweats finally began to appear and the patient soon entered the hospital.

Physical examination on admission showed signs of pneumonitis with fibrosis in the lower lobe of the left lung.

Roentgen examination showed pneumonitis in the lower lobe of the left lung. Within the infiltrated area there was a small cavity near the border of the heart at the level of the tenth rib posteriorly. An oblique view showed the presence of several air spaces which had the appearance of air cysts.

Bronchography with the aid of iodized poppy-seed oil (fig 5) showed marked dilatation of the bronchi in the lower lobe of the left lung. In addition, three collections of the iodized poppy-seed oil (2 by 3 cm) were interpreted as probably being due to the presence of bronchiectatic cysts.



It was the opinion of those who studied the case that the history was suspiciously like, but not clearly that of, putrid pulmonary abscess, that the various studies established the existence of bronchiectasis in the lower lobe of the left lung probably associated with cysts of the lung, and that an exploratory operation was justified to determine the exact status of the process

At operation, performed by Dr Harold Neuhof, thin pleural adhesions were observed overlying the pneumonic lower lobe of the left lung. After infiltrated lung tissue was traversed a smooth-lined pulmonary cyst containing some mucoid material was entered. A free bronchial communication was present. A primary putrid abscess of the lung was definitely ruled out by the exploration, and the diagnosis of cystic disease of the lung with secondary apparently transient putrid infection was clearly established.



Fig 5 (case 7)—Roentgenogram showing bronchiectatic air cysts along the left border of the heart partially outlined by iodized poppy-seed oil. The small cavity adjacent to the apex of the heart was shown at operation to be an infected air cyst.

CASE 8—A man aged 22 was admitted to the Mount Sinai Hospital on Jan 4, 1934, for a study of the pulmonary condition. Following an attack of epidemic influenza in 1918 he was left with a productive cough, which persisted without remission for seventeen years. The sputum was chiefly mucoid and was never foul or blood-tinged. From 1 to 4 ounces (30 to 120 cc) was expectorated daily. He felt entirely well otherwise and was able to lead a normal life.

On admission a general examination showed a well developed, well nourished man with no abnormalities other than those in the lungs and sinuses. In the right lung there were signs of infiltration in the upper lobe. The left lung was markedly contracted and presented signs of an extensive fibrocavernous process. The sinuses showed bilateral antral suppuration.

Roentgen examination of the chest (fig 6, left) disclosed a marked deformity of the thorax due to a contraction in the volume of the left lung and scoliosis of the dorsal vertebrae to the left. The left lung had about one-third its normal volume and appeared to be converted into a number of small and large honey-combed cavities, the largest of which was at the apex and measured about  $2\frac{1}{2}$  inches (6.5 cm) in diameter. The heart and mediastinum were displaced to the left. In the upper lobe of the right lung there was also a good deal of fibroid tissue with a number of small cavities within it. Bronchography (fig 6, right) clearly outlined many of the cavities seen in the ordinary film.

From the physical and roentgen examination it was not possible to make a differential diagnosis between chronic tuberculous and chronic nontuberculous fibrocystic disease of the lung.

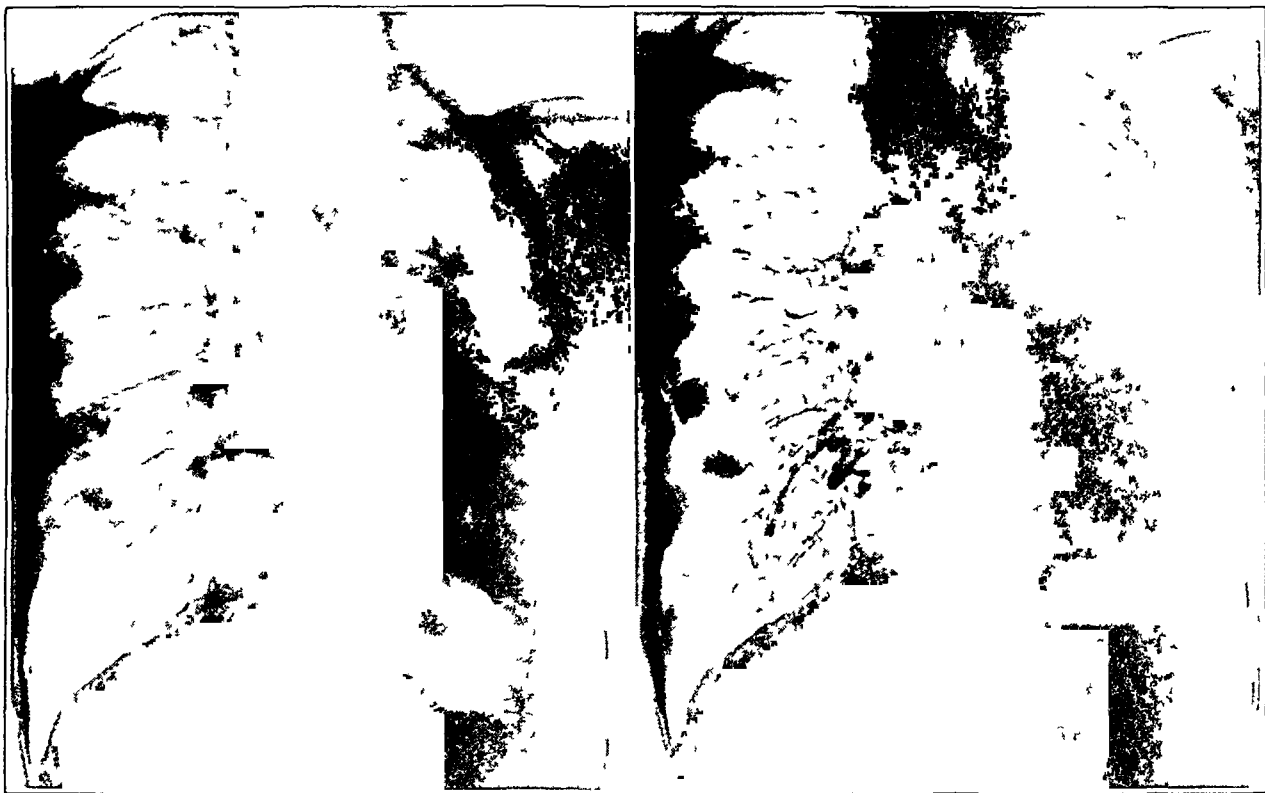


Fig 6 (case 8) —On the left is a roentgenogram showing a marked shrinkage in the volume of the left lung and numerous small and large honeycombed cavities in it. The right lung also shows considerable fibroid changes as well as a number of cavities. On the right is a bronchogram which shows many of the cavities outlined by iodized poppy-seed oil. Postmortem examination revealed that these cavities represented pulmonary cysts of the bronchiectatic variety.

There was no clubbing of the fingers. The sputum was mucopurulent and showed no tubercle bacilli on repeated tests. From 1 to 6 ounces (30 to 180 cc) was expectorated in twenty-four hours. The Wassermann reaction of the blood was negative.

During the first twelve days at the hospital the course was uneventful. Then erysipelas of the face developed, associated with marked constitutional symptoms. A few days later metastatic peritonitis developed, and the patient died after five days of acute illness.

At postmortem examination the left lung was observed to be a fibrous mass containing innumerable large and small cystlike cavities communicating with dilated

bronchi and lined in part with bronchial epithelium. There was not much evidence of functioning parenchyma in the left lung. The right lung showed small areas of bullous emphysema as well as bronchiectasis in the peripheral and lateral portion of the upper lobe, which was the seat of considerable fibrosis in the vicinity of a small area of healed tuberculosis. There was also extensive bilateral chronic pleuritis.

*Comment*—In cases 6, 7 and 8 cystic disease of the lung was associated with bronchiectasis and chronic pneumonitis of many years' duration. Obviously the chronic bronchopulmonary disease, which was characterized by extensive fibrosis replacing a good deal of the alveolar tissue, was the cause of the bronchiectasis as well as of the associated formation of cysts.

The recent superimposed and apparently transient anaerobic infection of the bronchiectatic cysts in case 7 produced the clinical picture of anaerobic pulmonary abscess. While the various preoperative studies suggested the probable nature of the pathologic process, an exploratory operation had to be resorted to in order to establish the correct diagnosis in that case.

Though a small tuberculous process was found in the upper lobe of the right lung in case 8, it is extremely doubtful if the extensive fibrocystic changes in the lungs could be explained on the basis of the tuberculous infection. It is more likely that the condition had its origin in the influenzal bronchopulmonary infection in 1918, which continued as chronic pneumonitis. The bronchiectatic and cystic disease was the sequel of the progressive destruction of the pulmonary parenchyma. In that instance the changes in the bronchi dominated the pathologic process, and the result was what might be termed the bronchiectatic form of cystic disease (as distinguished from the bullous form illustrated by case 3). In the right lung the process was apparently less advanced, and there bullous as well as bronchiectatic cysts were demonstrated, illustrating the mixed form of the disease.

#### PATHOLOGY AND PATHOGENESIS

Many theories have been advanced to explain the pathology and pathogenesis of cystic disease of the lung, almost as many as the number of authors who have written on the subject. Most of the theories postulate a congenital or acquired defect in the bronchi. Boyd<sup>3</sup> made no differentiation between the pathogenesis of bronchiectasis and that of cysts of the lung. De Lange<sup>4</sup> expressed the opinion that interference with the development of the alveolar tissue, which leaves the bronchi

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<sup>3</sup> Boyd, W. *The Pathology of Internal Diseases*, Philadelphia, Lea & Febiger, 1931, p. 191.

<sup>4</sup> de Lange, Cornelia. Angeborene Zystenlunge und agenetische Bronchiektasie, *Acta pædiat.* 6: 352, 1927.

unsupported, is responsible for the dilatation and the formation of cysts. According to Smith,<sup>5</sup> the cysts represent dilated atria. These views are fairly representative of the current opinion on the subject.

Generally speaking, there are two main types of architecture discernible in the structure of air cysts. (1) cysts the origin of which from bronchial dilatations can be readily demonstrated by the concentric arrangement of muscle fibers in the walls or the deposit of cartilage in them or by the lining of stratified ciliated columnar epithelium, and (2) cysts which resemble emphysematous blebs in appearance, essential structure and distribution. Between these two main types of cystic architecture there are all gradations of transitional forms in which both architectural patterns are intermingled to a greater or lesser degree.

The cysts may be solitary or multiple. The solitary or balloon cysts are usually encountered in infancy or early childhood and are rare. They are large and are usually fatal in early life. The multiple cysts are much more common, as a rule they produce relatively few or no symptoms and may be discovered only accidentally later in life. The cysts may vary greatly as to size, distribution, type of bronchial communication and nature of the contents. They may be small or large, they are usually confined to one lung but may be distributed in both, they may communicate with the bronchi either freely or through tortuous channels, and their cavities may be empty or may contain fluid, clear or otherwise. As to age incidence, cystic disease of the lung has been observed in patients of all ages.

From the point of view of origin, two types have been recognized: congenital and acquired. In early childhood the congenital origin of the lesion may not be difficult to establish. It is not always easy to determine whether a lesion is congenital or acquired when seen in an elderly patient. The recognized diagnostic criterion for the congenital origin is the absence of pigment in the involved lung, proving that the affected pulmonary parenchyma never functioned and that the pathologic condition must therefore have antedated birth. However, congenital lesions have occasionally been found adjacent to similar but acquired pathologic processes, as evidenced by the deposition of pigment in the affected pulmonary tissue.

A common associated condition in a cystic lung is pneumonitis and fibrosis of greater or lesser degree. This is invariably present in the acquired forms of the disease, as was shown in the cases which have been described. While pneumonitis and fibrosis are usually the cause of the cystic condition in the acquired form of the disease, it is not

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<sup>5</sup> Smith, S. Congenital Cystic Disease of the Lungs, *Brit. M. J.* **1** 1005 (May 30) 1925.

unlikely that in many cases they may be the result of the associated infection of the cysts

From a purely clinical point of view this paper is concerned with those forms of cystic disease of the lung, acquired or congenital, which produce symptoms and are likely to present diagnostic and therapeutic problems. The cases discussed in this paper show fairly representative forms of multiple cysts of the lung encountered in later life. The solitary or balloon cyst of the lung, which is usually encountered in infancy, has been described by a number of authors. The condition is characterized by acute episodes of dyspnea and cyanosis. The probable sequence of events was postulated by Parmelee and Apfelbach<sup>6</sup> as follows. There exists at birth a small congenital cyst which presents no signs or symptoms for a variable but usually a short period of time. Progressive enlargement of the cyst takes place in the course of time as a result of the increasing tortuosity of the bronchial communication with establishment of a check-valve type of bronchial opening. With the rapid increase in the size of the cyst there occurs a corresponding rise in its intracystic pressure, eventually leading to rupture. This results in a spontaneous tension pneumothorax, with marked dyspnea and cyanosis, which may end fatally.

#### SUMMARY

Cysts of the lung may present baffling diagnostic and therapeutic problems. Eight cases are presented illustrating the clinical features, the diagnosis, the therapeutic problems and the mechanism of the symptoms and signs of the condition. The chief complaints included recurring hemoptysis, episodes of pain in the chest and dyspnea, productive cough and foul expectoration.

Cystic disease of the lung may simulate the following common conditions: benign bronchial bleeding, pulmonary tuberculosis, tension pneumothorax, foreign body obstructive emphysema, bronchial neoplasm with stenosis, putrid pulmonary abscess and bronchiectasis.

The following pneumodynamic mechanisms were analyzed: (1) the development of an air cyst, as determined by aplasia or destruction of the surrounding pulmonary parenchyma, with resultant loss of elastic support, (2) the persistence or spontaneous disappearance of a cyst, as determined by the patency of its bronchial communication, (3) the growth and possible rupture of an air cyst, as determined by a check-valve type of bronchial communication, with a resultant progressive increase in the intracystic pressure, (4) the mechanism of chronic pneumothorax and its relation to recurring cystic rupture, (5) the mechanism of mediastinal displacement and bronchial distortion as pro-

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<sup>6</sup> Parmelee, A. H., and Apfelbach, C. W. Congenital Air Cyst of the Lung. *Am J Dis Child* **41**: 1380 (June) 1931.

duced by large cysts with a high intracystic pressure, and (6) the cause of recurring pain in the chest and dyspnea as related to the rupture of air cysts, with resulting tension pneumothorax

The congenital and acquired forms of cystic disease were characterized, and the difficulties encountered in their differentiation were pointed out

The following various types of pulmonary cysts were described (1) the large "balloon" cysts of early life, which are frequently fatal, and the multiple cysts of adult life, which may produce few or no symptoms, (2) the bullous cysts, the bronchiectatic cysts and the cysts with a mixed type of architecture, and (3) the clean and the infected cysts

The therapeutic procedures that are feasible in the treatment of the condition together with their rationale were briefly discussed. These included artificial pneumothorax, extirpation of the cysts and the injection of iodized poppy-seed oil or similar substances into the cystic cavity

# CONGENITAL AND FAMILIAL CLUBBING OF THE FINGERS AND TOES, WITH A POSSIBLY INHERITED TENDENCY

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Clubbing of the fingers and toes has been recognized as a clinical manifestation of intrathoracic disease from the earliest times. Hippocrates particularly described the condition as occurring with advanced phthisis and empyema and emphasized the importance of the changes as diagnostic of purulent pleural effusion. Many subsequent authors have described clubbing of the fingers associated with chronic disease of the heart or lungs, but it is still rare in medical literature to find the condition mentioned as being of primary origin. The present case is considered worthy of reporting not only because the simple clubbing of the hands and toes is apparently of primary origin but also because it is familial, possibly hereditary, is congenital as far as can be determined from the history and supposedly is the first instance of simple familial and congenital clubbing of the fingers and toes in a Negro to be described in medical literature.

## REPORT OF A CASE

The patient was a 44 year old Negro who had done hard labor all his life. He offered no chief complaint and the clubbing of the fingers and toes was discovered in a routine periodic health examination. Otherwise his general physical condition was entirely normal so far as could be determined by the usual methods of examination. A roentgenogram of the chest presented no evidence of pulmonary or cardiac disease. The Wassermann reaction was negative. The patient stated that he had had the clubbed fingers and toes as long as he could remember and that his mother told him that he had them when he was born<sup>1</sup>. His father (deceased) had similar clubbing, and his mother claimed that the father's condition was also congenital. The condition of the fingers and toes of his grandparents was unknown to the patient or to his mother. The patient had three brothers and one maternal half-brother who presented similar clubbing of the fingers and toes. All claimed to have had the condition as long as they could remember, and the mother stated that the condition was congenital in all. One brother whose fingers and toes were affected had two sons, 17 months and 2 months old. He described the infants' fingers as clubbed, but on examination of the children no true clubbing was found. There was, however, marked enlargement of the volar pads on the tips of the fingers, giving them the appearance of clubbed fingers from the ventral aspect. From the dorsal aspect the nails

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1 The veracity of this statement must be weighed in the light of the Negro's ability to observe pathologic conditions

presented none of the convexity of true clubbing. Pictures and roentgenograms were made of the infants' hands, and the children will be observed into later life to see whether or not clubbing of the fingers develops. The patient's mother and four sisters presented no clubbing of the fingers or toes.

#### REVIEW OF LITERATURE

In a review of the literature on primary congenital or familial clubbing of the fingers, reports of fourteen cases were found. As early as 1885 Mangelsdorf<sup>2</sup> reported a case of clubbed fingers without any apparent cause. Fraentzel<sup>3</sup> in 1888 described a case of clubbed fingers in a patient whose father and a healthy sister were likewise affected. In 1891, Freytag<sup>4</sup> observed two cases of primary clubbing of the fingers, in each of which the patient had a healthy father whose fingers were also clubbed. West<sup>5</sup> in 1897 commented on a case of clubbed fingers in a healthy white man aged 38. The clubbing was first noted at the age of 6 years. When the patient was 31 years old the clubbing suddenly, and with no apparent cause, became worse. West also observed clubbed fingers in a healthy woman 50 years old, in whom the condition was supposed to have commenced only three or four weeks previous to examination. In a third case of clubbing he could find no cause. Newton and Merrells<sup>6</sup> reported a case of simple clubbing of the fingers in a healthy white man, aged 33, with associated hypertrophic osteoarthropathy. The patient's paternal grandfather, brother, daughter and three dead children (the youngest died when 7 years old) presented the same condition. The patient's father, mother and sister had no clubbed fingers. The clubbing of the digits in this patient had always been proportional to the growth of the hands and feet. Decloux and Lippmann<sup>7</sup> described a patient with congenital primary clubbing of the fingers. One sister had a similar condition. Symons<sup>8</sup> likewise reported a case of primary clubbed fingers. Von Eiselsberg<sup>9</sup> described congenital and familial clubbing of the terminal phalanges in a white man 35 years old. One grandfather, one uncle and one sister of the patient had a similar condition. The author suggested that the origin of the clubbing might be of

2 Mangelsdorf, W. *Wien med Wchnschr* **35** 362, 1885.

3 Fraentzel, O. *Ueber Akromegalie*, *Deutsche med Wchnschr* **14** 651, 1888.

4 Freytag, A. *Ueber die Trommelschlagelfinger und Knochenveränderungen bei chronischen Lungen- und Herzkrankheiten*, Bonn, Hauptmann, 1891.

5 West, S. *Clubbed Fingers*, *Tr Clin Soc London* **30** 60, 1897.

6 Newton, R. C., and Merrells, E. *A Case of Pulmonary Osteo-Arthropathy*, *Internat Clin* **4** 153, 1902.

7 Decloux and Lippmann, A. *Osteo-Arthropathic Hypertrophie*, *Bull et mem Soc méd d hôp de Paris* **19** 80, 1902.

8 Symons, quoted by Locke<sup>20</sup>.

9 von Eiselsberg. *Munchen med Wchnschr* **58** 1591, 1911.



a "lymphangiomatous nature" In 1919 Weber<sup>10</sup> saw twin brothers, white, aged 25 years, with clubbed fingers The toes were not affected and there was no apparent visceral disease associated with the condition An elder brother, aged 30, had a similar condition The mother was unaffected, the father's condition was not known, there were no other brothers or sisters This author reported a second case, in a healthy white man, 25 years old, who had had the clubbed fingers and toes as long as he could remember His father, three brothers and one sister were similarly affected Lewy<sup>11</sup> in 1921 noted a case of congenital drumstick fingers Crouzon and Gutmann<sup>12</sup> described a case of primary clubbed fingers in a white man 30 years old The patient had always had the condition His father was also affected The patient did not know whether his father's condition was congenital or acquired, nor did he know the condition of his father's fingers at the time of the patient's conception Neurath<sup>13</sup> commented on a case of hereditary clubbing of the thumbs Recently Kayne<sup>14</sup> reported a case of familial clubbing of the fingers and toes in a white man 32 years old There were no physical signs of disease of the heart or lungs, and the roentgenogram showed the chest to be normal The patient had had the condition as long as he could remember His father and one brother were similarly affected, while his mother, two brothers and three sisters presented no evidence of clubbing Ragins and Freilich<sup>15</sup> described a case of familial, congenital clubbing of the fingers and toes in a white man 34 years old One sister, the father and a paternal uncle presented the same condition

#### COMMENT

Simple clubbing of the fingers and toes has always been of interest to clinicians, but it was not until the nineteenth century that the subject received sufficient attention to provide any accurate knowledge of the nature of the changes in the extremities and skeleton Pigeaux<sup>16</sup> in 1832 was the first to use the term "Hippocratic fingers" to describe the condition No alterations other than those in the fingers were mentioned

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10 Weber, F P The Occurrence of Clubbed Fingers in Healthy Persons as a Familial Peculiarity, *Brit M J* **2** 379 (Sept 20) 1919

11 Lewy, E Congenital Drumstick Fingers, *Med Klin* **17** 845, 1921

12 Crouzon, O, and Gutmann Hereditary Hypertrophic Fingers *Bull et mem Soc med d hôp de Paris* **47** 1765, 1931

13 Neurath, R Hereditary Clubbed Thumbs, *Wien klin Wchnschr* **45** 1210, 1932

14 Kayne, G G Familial Clubbing of Fingers and Toes, *Proc Roy Soc Med* **26** 270, 1933

15 Ragins, O B, and Freilich, E B Familial Congenital Clubbing of Fingers and Toes, *Ann Int Med* **6** 946, 1933

16 Pigeaux *Arch gen de med* **29** 174, 1832

in medical literature until 1889, when von Bamberger<sup>17</sup> described the general thickening and sclerosis of the long bones which is associated with clubbing of the fingers. In a second paper, in 1891,<sup>18</sup> the same author discussed at length the nature and extent of the changes in the bones and their relation to various diseases. In the meantime Marie,<sup>19</sup> in 1890, ignorant of von Bamberger's observations, published a full and accurate description of the process in the long bones and fingers. These two authors, noting especially the subperiosteal formation of new bone rather than the clubbing of the fingers, suggested the cumbersome name "secondary hypertrophic pulmonary osteo-arthritis" to describe the condition. Since then many equally awkward names have been offered in defining the process of change in the bones, but the original name, *hippocratic fingers*, has stood the test of time better than the others. Von Bamberger suggested that simple clubbing of the fingers and hypertrophic osteo-arthritis were closely associated and were probably the same pathologic process, presenting different stages of the same disease. Janeway<sup>20</sup> in 1903 reported several cases of hypertrophic osteo-arthritis and reviewed all the previous literature, while Locke<sup>21</sup> in 1915 and 1920 brought the survey of the literature up to date. No additional information has been advanced concerning the condition up to the present time, with the exception that Holger,<sup>22</sup> Schirmer<sup>23</sup> and Thomas<sup>24</sup> have suggested the term *acropachy* to describe the disease in its early stages.

#### DEFINITION

At the present time hypertrophic osteo-arthritis may be defined as a disease, generally of secondary nature, occurring in the course of various chronic conditions, characterized by a general and symmetrical hypertrophy of the distal phalanges and toes with resulting clubbing (*acropachy*), frequently accompanied by enlargement of some of the other bones in the hands and feet or by hypertrophy of the bones of the forearms and legs, and in the late stages, by involvement of the joints.

17 von Bamberger. *Wien klin Wchnschr* **2** 226, 1889.

18 von Bamberger, E. *Ueber Knochenveränderungen bei chronischen Lungen- und Herzkrankheiten*, *Ztschr f klin Med* **18** 193, 1891.

19 Marie, P. *De l'ostéo-arthrophathie hypertrophiante pneumique*, *Rev de méd Paris* **10** 1, 1890.

20 Janeway, T. C. *Hypertrophic Osteo-Arthropathy*, *Am J M Sc* **126** 563, 1903.

21 Locke, E. A. (a) *Secondary Hypertrophic Osteo-Arthropathy and Its Relation to Simple Club Fingers*, *Arch Int Med* **15** 659 (May) 1915, (b) *Hypertrophic Osteo-Arthropathy*, in Christian, H. A., and Mackenzie, J. *Oxford Medicine*, New York, Oxford University Press, 1920, vol 4, pt 2, p 431.

22 Holger, F. *Ueber Acropachia*, *Wien Arch f inn Med* **1** 35, 1920.

23 Schirmer, O. *Acropachia*, *Wien Arch f inn Med* **5** 345, 1923.

24 Thomas, H. M., Jr. *Acropachy*, *Arch Int Med* **51** 571, 1933.

The relation of hypertrophic osteo-arthropathy to simple clubbing or hippocratic fingers is interesting. Clubbed fingers exist in almost all of the instances of hypertrophic osteo-arthropathy, but they may also be present in their most characteristic form in association with a considerable number of pulmonary and cardiac diseases in which no involvement of the long bones is to be noted (Thayer<sup>25</sup>). Is the same cause at work in both instances, the one condition being simply a more advanced degree of the other? It is certainly true that the most clearly defined hippocratic fingers may exist entirely alone, while in some cases of well marked hypertrophic osteo-arthropathy the clubbing of the terminal phalanges may be by no means as characteristic. In his second paper von Bamberger<sup>18</sup> discussed the possible relationship of simple clubbing of the fingers to hypertrophic osteo-arthropathy and suggested that the former may be simply an early stage of the latter. The opinions expressed by subsequent authors differ widely. Some have regarded the two conditions as closely related, if not identical, while others have held that there is a distinct difference between the two and that they should be regarded as independent. The evidence is entirely in favor of the opinion that the two conditions are identical and according to Landis<sup>26</sup> may be summarized as follows: (1) The two conditions are found associated with the same group of primary diseases, (2) the type of clubbing in the two conditions is the same, the differences described being merely the result of difference in the stage of the process, (3) clubbing of the fingers invariably occurs in hypertrophic osteo-arthropathy, (4) many conditions which appear to be simple clubbing reveal on roentgen examination alterations in the long bones precisely the same as those seen in hypertrophic osteo-arthropathy.

According to Sternberg,<sup>27</sup> three clinical types of hypertrophic osteo-arthropathy may be described, as follows: (1) Clubbing of the fingers and toes without changes in the long bones and usually without subjective symptoms, (2) a combination of clubbing with painful thickening of the long bones, especially of the lower portion of the forearms and legs (this type was described by von Bamberger<sup>17</sup>), (3) a stage of the disease in which the condition is no longer a mere incident in the course of the primary disease but by reason of the conspicuous general deformities and severe symptoms itself comes to the foreground (Marie's type<sup>19</sup>). These groups, in the light of present knowledge, are clearly only different stages in the development of one disease, hypertrophic

25 Thayer, W. S. Hypertrophic Pulmonary Osteo-Arthropathy and Acromegaly, New York M. J. **63** 33, 1896.

26 Landis, H. R. M. Hypertrophic Pulmonary Osteo-Arthropathy, with a Report of Two Cases, Penn. M. J. **10** 852, 1907.

27 Sternberg, M. in Nothnagel, C. W. H. Spezielle Pathologie und Therapie, Vienna, A. Holder, 1903, vol. 7, pt. 2, p. 72.

osteo-arthropathy Locke <sup>21b</sup> watched the advancement of the process through its different stages. In making the study reported in this paper my interest has been primarily with the first type of the disease, namely, simple clubbing of the fingers and toes without any changes in the long bones.

In the congenital or familial type of clubbing of the fingers, there does not seem to be any progressive tendency of the disease to develop into the hypertrophic osteo-arthropathic type, at least, no such case was reported in the literature. Five cases (Gluzinski,<sup>28</sup> Reed,<sup>29</sup> Soltau,<sup>30</sup> Symons,<sup>8</sup> van der Weijde and Boekhoudt<sup>31</sup>) which were apparently instances of primary hypertrophic osteo-arthropathy were reported up to Oct 3, 1914 (Locke <sup>21a</sup>), and no mention of a subsequent case was found other than that reported by Thomas,<sup>24</sup> in which the condition followed a subtotal thyroidectomy. The evidence is overwhelming that hypertrophic osteo-arthropathy is secondary to some visceral disease, usually pulmonary or cardiac, yet an occasional case has been reported in which it followed disease of the abdominal viscera, blood dyscrasia or involvement of the thyroid. In the cases in which the phenomena have existed since birth and have been present in other members of the family, one must either beg the question or postulate some peculiar susceptibility of the osseous system. That great individual differences in the reaction of bones to irritants exist is evident from the varying time required for the repair of fractures. In the case reported here, in which the condition was apparently primary and had an inherited or congenital and familial association, there has been no progression of the clubbing process other than the proportional enlargement of the terminal phalanges with the growth of the hands.

Hypertrophic osteo-arthropathy and simple clubbing of the fingers are much more prevalent in men than in women, in Thompson's<sup>32</sup> series they occurred in men in 86 per cent of the cases. That hypertrophic osteo-arthropathy is not necessarily a disease specific to the human race is evidenced by the report of Ball and Lombard,<sup>33</sup> who

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28 Gluzinski, A. Osteo-Arthropathie Hypertrophiante Mariego, *Przegł lek* **1** 480, 1811.

29 Reed, E. P. Un caso de osteo-arthropatia hipertrofiante de origen neuromico, *Rev med de Chile* **32** 199, 1904.

30 Soltau. A Case of Chronic Hypertrophic Osteo-Arthropathy, *Tr Clin Soc London* **34** 249, 1901.

31 van der Weijde, A. J., and Boekhoudt, H. B. Een geval van osteo-arthropathie hypertrophiante, *Nederl tijdschr v geneesk* **31** 781, 1895.

32 Thompson, H. E. S. Hypertrophic Pulmonary Osteo-Arthropathy, *Med Chir Tr, London* **87** 85, 1904.

33 Ball, V., and Lombard, C. Hypertrophic Pulmonary Osteo-Arthropathy in Wild Animals in Captivity, *Bull Acad de med Paris* **95** 16, 1926.

observed the condition in a 10 year old captive lioness with pulmonary tuberculosis. Ball and Alamartine<sup>34</sup> described a similar condition in tuberculous dogs.

#### PATHOLOGIC CHANGES IN CLUBBING OF THE FINGERS

In the average case of simple clubbed fingers, as in this reported case (fig 1), the deformity is sharply confined to the distal phalanges and is almost strictly symmetrical. The thumbs and forefingers are commonly the first attacked, and hence when the condition has reached an advanced stage they are likely to present a considerably greater degree of deformity than is shown by the other fingers. The most striking feature is the bulbous enlargement of the terminal phalanges of the fingers and toes, which is largely due to changes in the soft parts. The clubbing begins just beyond the interphalangeal joint as a definite firm transverse ridge, most marked on the dorsal aspect but extending onto the lateral surfaces of the fingers. On the palmar side

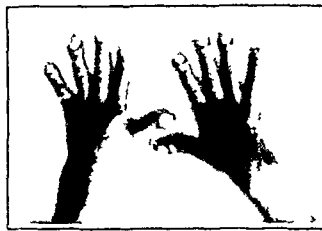


Fig 1—Photograph of the hands of a Negro showing clubbing of the fingers

the increase in size is more gradual. The whole finger beyond the ridge is bulbous or drumstick-like. The overlying skin is smooth and shiny. The nails are greatly thickened, ridged longitudinally and curved in both directions, sometimes to such an extent as to offer a close resemblance to a parrot's beak. Corper and Cosman<sup>35</sup> described the hyperconvexity of the nail, and Lefebvre<sup>36</sup> likened it to a watch glass fitted on the end of the finger. The nail bed is full, rounded, smooth, cyanotic and injected. The sluggish circulation is apparent from slow return of color after slight pressure on the nail. The base of the nail lies above the level of the knuckle, so that its outline can be discerned

34 Ball, V, and Alamartine, H. Les lésions broncho-pulmonaires dans l'ostéo-arthropathie hypertrophiante pneumonique du chien, étiologie et pathogénie du syndrome de P. Marie envisagé comme une tuberculose inflammatoire, *J. d. med. vet. et de zootech.* **17** 1, 1913.

35 Corper, H. J., and Cosman, P. Hypertrophic Osteo-Arthropathy in Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **5** 357, 1921.

36 Lefebvre, A. Des déformations ostéo-articulaires, consécutives à des maladies de l'appareil pleuro-pulmonaire (ostéo-arthropathie hypertrophiante-pneumonique de P. Marie), Paris, Félix Alcan, 1891.

beneath the skin. When the nail is pressed at either end, it rocks up and down, giving the impression that it is fastened only at its center and that it is floating. Normally the root of the nail is attached to the phalangeal periosteum. Hyperextension of the terminal phalanx associated with clubbing of the fingers was first described by Marie<sup>19</sup> and has subsequently been reported by other observers. In the early stages of clubbing, slight curving, slight cyanosis and mobility of the nail root occur before the obvious swelling or clubbing. A significant early change is an unusual smoothness or shininess of the skin behind the nail and over the root of the nail.

In a few cases clubbed fingers have been examined microscopically but no two observers have agreed as to the essential changes in the soft parts. It is not surprising, therefore, that there is considerable difficulty in offering a satisfactory explanation of the manner in which clubbing arises, and this difficulty is certainly not diminished by the extraordinary number of diseases in which the deformity appears. Campbell<sup>37</sup> presented longitudinal photomicrographs of a clubbed finger and noted a distinct thickening of the tissue between the nail and phalanx, due to the presence of excessive edema. The fibrils of the connective tissue, instead of running in compact bundles as in normal fingers, were widely separated from each other in many places. There was no fibrous thickening of the rete mucosum, no increase in the connective tissue (though he stated that if the edema persists long enough increase in the connective tissue will result) and no excess of fat. Campbell<sup>37</sup> concluded that the essential difference between the clubbed and the normal finger was the edematous condition of the tissue lying between the nail bed and the bone. Freytag<sup>4</sup> noted dilatation of the capillary loops in the nail bed, with engorgement of the interpapillary processes, but noted no alteration in the skin, no endarteritis obliterans and no thickening of the nerve sheaths. Thérièse<sup>38</sup> commented on the hypertrophy of the horny layer, papillae, and connective tissue of the derma. Buzzard<sup>39</sup> observed mainly an excess of subcutaneous fat in the bulbous fingers. From the study of a microscopic section of a clubbed finger, Schirmer<sup>23</sup> noted a tissue resembling embryonic mucoid tissue. Thomas<sup>24</sup> observed marked dilatation of the venous side of the capillaries of the nail bed and an extreme degree of tortuosity of the arterial side.

37 Campbell, D. Hippocratic Fingers, *Brit M J* **1** 145 1924

38 Therèse, L. Ostéo-arthrite hypertrophiante pneumonique. Examen histologique et chimique des os de l'avant bras, *Bull Soc anat de Paris* **66** 143 (Feb) 1891

39 Buzzard, E. F. Sequel to a Case of Pulmonary Hypertrophic Osteo-Arthropathy, *Necropsy Brit M J* **1** 1333 (June 1) 1901

## ROENTGENOLOGIC STUDY OF CLUBBED FINGERS

It is generally stated that the typical bulbous enlargement of the terminal phalanges of the fingers and toes is entirely due to changes in the soft parts. This is undoubtedly true in the majority of cases of clubbed fingers in which there are no changes in the long bones, although in a few cases in which roentgen examination was made there was an unmistakable alteration in the distal phalanges. It must be always borne in mind, however, that the ungual phalanges in healthy persons present extreme variations in size and shape. Locke<sup>21</sup> studied thirty-nine cases of apparently simple clubbing and found that roentgen examination revealed a definite proliferation of the bone of the distal phalanges in five instances. Many other authors (Kessel,<sup>40</sup> Corper and Cosman,<sup>35</sup> Thomas,<sup>24</sup> Goulesbrough,<sup>41</sup> Singer,<sup>42</sup> Hyman and Herrick<sup>43</sup>) described similar changes as rarely, though definitely, occurring



Fig 2—Roentgenogram of clubbed fingers showing spatulation of the bone in the distal half of the terminal phalanges

in simple clubbed fingers. In the familial type of clubbing of the fingers Ragins and Freilich<sup>15</sup> observed the distal bony phalanges to be enlarged, and Kayne<sup>14</sup> commented on the terminal phalanges being splayed out. In the case reported here definite spatulation of the distal halves of the ungual phalanges was readily noted (fig 2).

In the more advanced cases in which there are changes in the long bones the hypertrophy of the terminal bones of the fingers is much more common and marked. The age of the patient is also important in noting

40 Kessel, L. Hypertrophic Osteo-Arthropathy, *Arch Int Med* **19** 239 (Feb) 1917

41 Goulesbrough, C. Pulmonary Osteo-Arthropathy, *Arch Roentg Ray* **18** 208, 1913

42 Singer, S. Drumstick Fingers with Peculiar Bony Changes, *Wien med Wchnschr* **78** 226, 1928

43 Hyman, C. H., and Herrick, T. P. Chronic Osteo-Arthropathy in a Child, *J A M A* **78** 1043 (April 8) 1922

any changes of the bone, as periosteal reactions are more easily stimulated in a child. Walters,<sup>44</sup> however, observed fetal clubbing of the fingers (fetal age not given) associated with congenital heart disease, and noted no bony changes. The alterations in the end-phalanges are in the nature of an irregular mossy proliferation confined chiefly to the distal half, giving to the bone a "bur-like" appearance. Rarely, long spurlike projections (osteophytes) are found at the proximal ends of the distal phalanges, near the line of the joint cartilage (Locke<sup>21a</sup>).

Thompson<sup>32</sup> reported that chemical examination of the affected bone in hypertrophic osteo-arthropathy showed a marked increase in magnesium phosphate at the expense of the calcium salts, with increase in the organic matter.

Brooks<sup>45</sup> cited several cases of hypertrophic osteo-arthropathy with bulbous enlargement of the nose and thickening of the subcutaneous tissues of the malar regions. No such changes were observed in the case of simple clubbing reported here. Corpe and Cosman,<sup>35</sup> when studying clubbing of the fingers in pulmonary tuberculosis, observed in many instances a peculiar nodular tumor on the hard palate in the midline, extending to the junction of the hard and the soft palate. There were no symptoms except change of speech, although roentgen examination revealed changes of the bone in the maxilla and hard palate. No such changes were noted in the case reported here.

#### ETIOLOGY

The etiology of simple clubbing of the fingers and toes and of hypertrophic osteo-arthropathy has been a cause of concern to clinicians for many years. As early as 1832 Pigeaux<sup>16</sup> considered clubbing of the fingers as due to a local circulatory disturbance with a consequent edematous swelling and heaping up of the nail matrix. He thought that if the nail matrix was raised above the nail bed the nail must grow downward toward the palmar surface of the finger. That dilatation of the capillaries in the nail bed occurs in simple clubbing of the fingers is generally accepted. The continued peripheral hyperemia is produced by compression of the capillaries of the lung or by obstruction of the venous return. The capillaries, already being subjected to increased hydrostatic pressure, become chronically engorged. The hyperemia gives the extremities their cyanotic appearance and later brings about a proliferation of the distal phalanges of the fingers and toes. The capillaries supplying the phalangeal periosteum may be the first to

44 Walters, F. R. A Case of Hyperplastic Osteo-Arthritis, or Pulmonary Hypertrophic Osteo-Arthropathy of Marie, *St. Thomas's Hosp. Rep.* **24** 105, 1897.

45 Brooks, H. A Discussion of the Pathogenesis of Hypertrophic Pulmonary Osteo-arthropathy, *New York M. J.* **94** 608, 1913.



become involved, with resultant fibroblastic and osteoblastic stimulation, and the deposition of the layer of subperiosteal new bone typical of hypertrophic osteo-arthropathy. The digital pulp undergoes an increase, giving the fingers their typical drumstick appearance.

In support of the theory that venous obstruction, with resultant capillary hyperemia, is the cause of clubbing of the fingers, Campbell<sup>37</sup> cited instances in which elevation of the limb for several days reduced the clubbing while ligation of the subclavian artery almost caused the clubbing to disappear. Souques<sup>46</sup> reported a case of unilateral clubbing in which the veins in the arm above were markedly varicose, and Thomas<sup>24</sup> commented on clubbing resulting from alteration of the circulation in sudden reduction of the metabolic rate. Even though it may be objected that clubbing of the toes is not a sequel to unilateral thrombophlebitis, the theory that mechanical obstruction is the sole etiologic factor of clubbing is difficult to accept. In the first place, clubbing is not edema, and it is hardly ever noted in association with edema, or in cases in which cyanosis and central obstruction are considerable, as in diseases of the heart other than congenital disorders, intrathoracic tumors, etc. Clubbing occurs in many cases of thoracic disease in which there is no obvious interference with the circulation, as in chronic empyema, and occasionally in abdominal conditions in which the thorax is entirely free from disease. It may occur in persons who are otherwise in perfect health (West<sup>5</sup>).

That defective oxygenation of the blood may also play a rôle in clubbing is possible, since it is well known that suboxygenated blood or passive congestion invites hyperplasia of abnormal tissue, as witness the interstitial hyperplasia in chronic congestive diseases of the liver and spleen. This conception is capable of wider application and will explain the clubbing so frequently seen in cases of congenital heart disease. In this condition clubbing occurs more especially in cases of pulmonary stenosis, with a patent foramen ovale and an incomplete intraventricular septum. It is to be noted that congenital disease is the condition most frequently associated with cyanosis. Anoxemia also explains the clubbing associated with dyscrasias of the blood, and the "autotoxic enterogenous cyanosis" (Campbell<sup>37</sup>), in which there is either methemoglobin or sulfhemoglobin in the blood resulting from the absorption of the products of intestinal putrefaction.

An objection can be made against anoxemia as the cause of clubbing. If an insufficient supply of oxygen to the tissues is an important etiologic factor in clubbing, why has clubbing not been found in cases of long standing severe anemia? Thomas<sup>24</sup> suggested that it may be that the

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46 Souques, A. Pathogenesis of Hippocratic Fingers, *Bull et mem Soc med d hôp de Paris* **43** 186, 1919.

adjustment of tissues to anemia is gradual, whereas in simple clubbing time for this adjustment is lacking

Marie<sup>19</sup> strongly advocated the theory that clubbing is due to toxins. He summarized the cycle of changes under three headings: (1) A lesion of the respiratory apparatus, allowing the production of putrid or fermenting substances under the influence of micro-organisms, (2) the absorption and passage of these products into the general circulation, (3) an elective action of these substances on certain parts of the bones and joints.

It is evident from the fact that the disease occurs in association with certain lesions of the heart and with other conditions in which no form of suppuration exists that the theory that clubbing is due to circulating toxins alone will not fit all cases. It is also important to point out other obvious objections in considering circulating toxins the cause of clubbing. Thomas<sup>24</sup> asked why, for instance, an abscess of the lung should produce such a toxin if abscesses elsewhere in the body do not produce it. Why should clubbing occur with carcinoma of the bronchus and not with carcinoma in other parts of the body? Why should the toxin be liberated in pulmonary tuberculosis and not in tuberculosis of other organs?

Béclère<sup>47</sup> has combined the two theories of clubbing into a mechanotoxic hypothesis. He considered that venous blood naturally contains substances which provoke changes in the fingers and that if during its passage through the lungs these substances are not removed from the blood clubbing results.

The occasional association of clubbing of the fingers with certain nervous diseases has suggested a possible relationship between hypertrophic osteo-arthropathy and diseases of the nervous system. Several authors (Hirshfeld,<sup>48</sup> Janeway<sup>20</sup> and Mobius) have written in favor of such an etiologic relationship. Wynn<sup>49</sup> observed no gross lesion of the central nervous system in the cases cited and in the few instances in which the nerves had been especially examined. Any changes found have been easily explained. Moreover, in those cases of clubbing of the fingers associated with neuritis due to injury there were always marked trophic changes in the skin which did not occur in cases of simple clubbing.

Godlee<sup>50</sup> regarded hypertrophic osteo-arthropathy as due to syphilis, but later writers have been unable to find sufficient evidence for such

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47 Béclère, A. *Semaine méd* **21** 94, 1901

48 Hirshfeld. *Ueber Vergrosserungen der Hande und Fusse auf neuritischer Grundlage*, *Ztschr f klin Med* **44** 5 and 251, 1902

49 Wynn, W. H. *Secondary Hypertrophic Pulmonary Osteo-Arthropathy*, *Birmingham M Rev* **55** 139, 1904

50 Godlee, H. J. *Bone and Joint Changes in Connection with Thoracic Disease*, *Brit M J* **2** 57, 116 and 1417, 1896

a claim Thorburn<sup>51</sup> suggested that clubbing is actually of a tuberculous nature, but "of a benign type, having no tendency to break down and caseate" Massalongo<sup>52</sup> expressed the belief that clubbing is the "consequence of causes acting contemporaneously or alone, among which the arthritic diathesis plays the principal rôle"

Cummins<sup>53</sup> demonstrated the presence of volar padding of the terminal phalanges in the third fetal month. In the last half of gestation regression occurs, which results in contours of the hand comparable to those of the adult. Persistence of the volar pads into infant life, as seen in the nephew of the patient described here, might offer a possible explanation of congenital clubbing.

Higier<sup>54</sup> observed in Warsaw, in the last half of 1917, seventy cases of osteo-arthropathy, osteomalacia and late rachitis in an endemic form. He thought that lack of vitamin A was the cause.

Thayer,<sup>25</sup> Ronchetti,<sup>55</sup> and others compared hypertrophic osteo-arthropathy to amyloid degeneration, which in certain unexplained conditions follows or accompanies protracted suppuration.

Clubbing is manifestly more likely to be carried on to a marked degree in young tissues, which are physiologically most inclined to hyperplastic growth. Hence it is that the changes due to clubbing are more pronounced in youth than in adult life or in old age.

From all of the theories as to the etiology of clubbing, it is most generally accepted that clubbing is the result of altered flow of blood, defective oxidation or hyperemia in the tissues of the extremities, whether produced mechanically by obstruction to venous return or as a result of a general lowering of the oxygen tension of the blood affecting parts of the body where normally circulation is slow. The altered flow of blood offers itself as the most plausible common etiologic factor.

Considering the difficulty of explaining the etiology of clubbing of the fingers secondary to some visceral disease, it is readily understood that the etiology of primary clubbing is all the more vague, especially in cases in which the condition is apparently congenital and definitely familial.

51 Thorburn, W. Three Cases of Hypertrophic Pulmonary Osteo-Arthropathy, *Brit M J* **1** 1155, 1893.

52 Massalongo, R. Osteo-artropatia ipertrofica pneumica, *Policlinico (sez med)* **4** 512, 1897.

53 Cummins, H. The Topographic History of Volar Pads (Walking Pads, Tastwallen) in The Human Embryo, *Contrib Embryol* (no 113) **20** 103 (Jan) 1929.

54 Higier, H. Endemic Osteo-Arthropathy, *Ztschr f klin Med* **95** 445, 1922.

55 Ronchetti, V. Club Fingers and Leukocytosis as Symptoms of Hepatic and Amyloid Degeneration, *Osp maggiore* **18** 1 (Jan) 1930.

## EXPERIMENTAL STUDY

A limited amount of experimental work has been done to produce clubbed fingers. Wegner (cited by Locke <sup>21a</sup>) showed that small doses of phosphorus caused a formative stimulation of the periosteum. Similar results were obtained by Gil (cited by Locke <sup>21a</sup>) in animals fed arsenic. Von Bamberger <sup>18</sup> attempted to produce the lesions of hypertrophic osteo-arthritis in rabbits by injecting bronchiectatic sputum into the rectum, but his results were negative. Herz, <sup>56</sup> by experimentally widening the capillaries of the nail bed, produced clubbing of the fingers. Campbell, <sup>37</sup> as noted previously, observed that elevation of the arm for several days reduced the clubbing, while ligation of the subclavian artery almost entirely removed it. Compere, Adams and Compere <sup>57</sup> were unsuccessful in reproducing periosteal changes in dogs when paraffin had been injected into the lungs.

## ONSET AND PROGNOSIS

Clubbing of the fingers usually is of insidious onset, yet Ebstein <sup>58</sup> has noted its appearance within a single week. Pain, lividity and numbness of the finger-tips accompanied the rapid onset. West <sup>5</sup> reported a case in which clubbing developed in two weeks.

The prognosis of the condition is dependent entirely on the course of the primary disease. Often there is a characteristic irregular clinical course of exacerbations and remissions following increased activity or improvement in the primary disease. The fluctuations in local signs are largely due to changes in the soft parts, although it is possible that in many instances a similar variation, but of less marked degree, takes place in the osseous tissue as well (Locke <sup>21a</sup>). It has been reported that in some of the early and acute cases of clubbing complete regression has been observed with cure of the primary disease. It is probable, however, that when the hypertrophic osteo-arthritis has passed the first stage the retrogression is never complete.

In the case of possibly inherited, congenital and familial clubbing reported here and in similar cases reported in the literature, there has been no progressive or regressive tendency of the process. This type of clubbing, once it has occurred, appears to be limited in its progressive development but is permanent.

## CONCLUSION

As West <sup>5</sup> has so aptly described the condition, clubbing is one of those phenomena with which all physicians are so familiar that they appear to know more about it than they really do.

<sup>56</sup> Herz. *Verhandl kong f inn Med*, 1896, p. 466.

<sup>57</sup> Compere, E. L., Adams, W. E., and Compere, C. L. Possible Etiological Factors in the Production of Pulmonary Osteo-Arthritis, *Proc Soc Exper Biol & Med* **28** 1083 (June) 1931.

<sup>58</sup> Ebstein, E. *Deutsches Arch f klin Med* **89** 67, 1907.

# EFFECT OF ERGOTAMINE TARTRATE ON PRESSURE OF CEREBROSPINAL FLUID AND BLOOD DURING MIGRAINE HEADACHE

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During the last few years a half-dozen reports have appeared in the French and German literature concerning the value of ergotamine tartrate (gynergen) in the treatment of migraine. A summary of the literature as well as of the therapeutic results obtained with forty-five of his own patients has been made recently by Lennox<sup>1</sup>. All the authors who have studied the subject agree that in the great majority of patients suffering from migraine headache the injection of ergotamine tartrate cuts short the attack, an action which seems to be specific, or nearly so, for headache of the migraine type.

The authors who have reported these dramatic clinical results have offered theories but little or no evidence concerning the mechanism by which ergotamine acts. A study of the physiologic effects of ergotamine on patients during a migraine headache might, we thought, uncover the cause of the relief and hence suggest the cause of the migraine. With this thought in mind, we have observed the effects of ergotamine tartrate on the pressure of the cerebrospinal fluid and of the arterial blood, on the rate of the heart and on the symptoms of patients who were suffering from an attack of migraine. As a control, similar observations were made on a group of patients not subject to migraine.

Ergotamine is the most recently isolated active principle of ergot having been separated from ergot in 1918 by Stoll<sup>2</sup>. A specific alkaloid with the formula  $C_{33}H_{35}N_5O_5$ , it is similar to, though not identical with, ergotoxine  $C_{35}H_{41}N_5O_6$ <sup>3</sup>. Ergotamine tartrate (gynergen)<sup>4</sup> is a stable

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This investigation was aided by a grant of the Josiah Macy Jr. Foundation. From the Neurological Service of the Boston City Hospital and the Department of Neuropathology of the Harvard Medical School.

1 Lennox, W. G. The Use of Ergotamine Tartrate in Migraine, New England J. Med. **210** 1061 (May 17) 1934.

2 Spiro, K., and Stoll, A. Ueber die wirksamen Substanzen des Mutterkorns, Schweiz. med. Wchnschr. **51** 525, 1921.

3 Cohen, M. S., and Githens, T. S. Pharmacotherapeutics, New York, D. Appleton & Company, 1928.

4 The Sandoz Chemical Works, Inc., supplied the drug used in this investigation.

salt dispensed in ampules suitable for parenteral injection. The intravenous dosage for acute attacks of migraine ranges from 0.5 to 1 cc (from 0.25 to 0.5 mg). While ergotamine may produce nausea and vomiting, and occasionally a feeling of constriction in the chest, other untoward results are usually the consequence of excessive dosage.

Ergotamine has been the subject of numerous pharmacologic and physiologic investigations. Dale's<sup>5</sup> comprehensive work in 1906 showed that the intravenous injection of ergot in animals raised their blood pressure, apparently by a peripheral vasoconstrictive action, and reversed the usual pressor effect of epinephrine and that large doses of ergot paralyzed, while small doses stimulated, sympathetic nerve endings. Rothlin<sup>6</sup> demonstrated that ergotamine in large doses exerts a peripheral action as a depressant of the sympathetic innervation and may inhibit or reverse the effect of epinephrine on the blood pressure and heart and that it augments smooth muscle tone, as indicated by experiments on the isolated uterus and intestine. Koppányi and Evans<sup>7</sup> demonstrated that ergotamine exerts its emetic action through peripheral stimulation of the gastro-intestinal tract. Andrus and Martin<sup>8</sup> conclusively demonstrated in dogs and cats a slowing of the sinus rhythm and of the auriculoventricular conduction time of the denervated heart through depression of the cardiac sympathetic end-organs. Mendez<sup>9</sup> stated the belief that ergotamine depresses the stimulatory but not the inhibitory action of epinephrine. Heymans<sup>10</sup> showed that intravenous administration of ergotamine causes vasoconstriction, Cannon and Bacq<sup>11</sup> demonstrated that ergotoxine prevents the normal manifestations of sympa-

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5 Dale, H. H. On Some Physiological Actions of Ergot, *J. Physiol.* **34**, 163, 1906.

6 Rothlin, E. Ueber die pharmakologische und therapeutische Wirkung des Ergotamins auf den Sympathicus, *Klin. Wchnschr.* **4** 1437, 1925, Contribution à la méthode chimique d'exploration du système sympathique, *Rev. neurol.* **33** 1108 (June) 1926, Influence de l'ergotamine sur les fonctions sympathiques, *Sc. méd.*, June 15, 1926, The Specific Action of Ergot Alkaloids on the Sympathetic Nervous System, *J. Pharmacol. & Exper. Therapy* **36** 657, 1929, Zur Pharmakologie des vegetativen Nervensystems, *Schweiz. med. Wchnschr.* **60** 1001, 1930.

7 Koppányi, T., and Evans, E. I. Studies on Emetic and Anti-Emetic Actions of Ergotamine, *Proc. Soc. Exper. Biol. & Med.* **29** 1181 (June) 1932.

8 Andrus, E. C., and Martin, L. E. The Action of the Sympathetic on the Excitatory Process in the Mammalian Heart, *J. Exper. Med.* **45** 1017 (June) 1927.

9 Mendez, R. Antagonism of Adrenaline by Ergotamine, *J. Pharmacol. & Exper. Therap.* **32** 451 (April) 1928.

10 Heymans, C., Bouckaert, J. J., and Morass, A. Au sujet de l'action vasculaire de l'ergotamine. Inversion de l'action vasoconstrictrice de "vasotonics" du sang défibriné par l'ergotamine, *Compt. rend. Soc. de biol.* **110** 993, 1932.

11 Cannon, W. B., and Bacq, Z. M. Hormone Produced by Sympathetic Action on Smooth Muscle, *Am. J. Physiol.* **96** 392, 1931.

thetic stimulation but does not hinder the liberation of "sympathin" from the stimulated organs. Clark,<sup>12</sup> also working with ergotoxine, found that it may reverse the vasoconstrictive action of epinephrine in the intestines but not in the skin. Woods and the Nelsons<sup>13</sup> corroborated the latter findings with ergotamine. Its effect was more marked in the splanchnic area than in the vessels of the nasal mucosa.

To summarize the physiologic and pharmacologic effects of ergotamine tartrate, it may be said that the drug stimulates smooth muscle, depresses peripheral sympathetic nerve endings, especially those in the splanchnic area and may act as an antagonist of epinephrine. The effect of ergotamine on the sympathetic nervous system has been likened to that of atropine on the parasympathetic system.

One of the theories concerning the etiology of migraine (that of the cerebral vascular spasm) is summarized and discussed by Riley<sup>14</sup> in his excellent review of migraine and by Robey<sup>15</sup> in his treatise on headache. Because it has long been recognized that vasoconstriction may be produced by sympathetic activity, it has been assumed that the spasm of vessels might be relieved by a depressant of sympathetic nerves. This is the explanation advanced by those European writers who have used ergotamine tartrate in the treatment of migraine. If migraine headaches are indeed due to vascular spasm and this spasm is released by ergotamine, there should be changes in the pressure of the blood and of the spinal fluid coincident with the relief of the headache. In this study we have sought for such evidence.

#### METHOD

Twenty-seven persons were studied, of whom sixteen were women and eleven men. Observations were made on the spinal fluid pressure, on the blood pressure and on the pulse rate before and after the administration of ergotamine tartrate (or saline solution). Eleven subjects were patients who were having an acute attack of headache. The remaining sixteen patients were not subject to attacks and served as a control group. Twelve of these were given ergotamine tartrate, four were given a small intravenous injection of sterile physiologic solution of sodium chloride. A total of thirty-one records was obtained from the twenty-seven patients. On three of the patients who had migraine headaches observations on the pulse rate and blood pressure were made at a time other than that in which the spinal fluid pressure was being recorded. The full observations were not made in every case. Of the thirty-one experiments, the blood pressure was studied in twenty-five, the spinal fluid pressure in twenty-three and the pulse rate in twenty. The detailed observations appear in the accompanying tables.

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12 Clark, G. A. *J. Physiol.* **80** 429, 1934.

13 Woods, G. G., Nelson, V. F., and Nelson, E. E. Effect of Small Amounts of Ergotamine on the Circulatory Response to Epinephrine, *J. Pharmacol. & Exper. Therap.* **45** 403, 1932.

14 Riley, H. A. Migraine, *Bull. Neurol. Inst. New York* **2** 429 (Nov.) 1932.

15 Robey, W. H. Headache, Philadelphia, J. B. Lippincott Company, 1931.

Records of blood pressure and pulse rate were made at intervals of a few minutes. The spinal fluid pressure was observed continuously in an Ayer spinal fluid manometer with an open end attached to a three way Fremont-Smith lumbar needle by small bore rubber tubing. The entire system of manometer and tubing was first filled with sterile physiologic solution of sodium chloride to atmospheric pressure to avoid loss of spinal fluid into the apparatus. The patient lay on the left side. No record of spinal fluid pressure was made unless there were oscillations of the spinal fluid pressure reflecting the pulse, the respiration and the compression of the abdominal and jugular veins. A short period of hyperpnea (thirty deep breaths), with a consequent temporary lowering of the level of spinal fluid pressure, was often resorted to at the onset of observations in order to ensure a minimum pressure. Readings for spinal fluid pressure were recorded when the pressure had resumed a constant level after completion of the various dynamic tests or of hyperpnea. Throughout each experiment, the highest and lowest pressures for each minute were recorded and subsequently plotted. In all cases, basal levels of spinal fluid pressure, blood pressure and pulse rate were recorded for a period ranging from ten to seventy minutes previous to medication. The total periods of observation varied from one and one-half to three hours and in the cases of migraine included the disappearance time of the headache (with the exception of the two unrelieved patients). The occurrence and time relations of headaches, nausea, vomiting and irregularity in the rhythm of the pulse were noted.

The diagnosis of migraine was made on the history of periodic headaches recurring over a number of years, resistant to therapy and usually but not necessarily associated with nausea, sometimes with vomiting, sometimes with visual disturbances and always with marked general distress or prostration. The family history in all cases suggested a hereditary predisposition. The results of routine examinations of the blood and spinal fluid of the patients were normal.

## RESULTS

*Clinical Effects*—In addition to the observations listed in tables 1 and 2, the following symptoms were noted. Of the fifteen patients who had migraine, seven experienced nausea and all but one vomited after the administration of ergotamine tartrate. Of the twelve control subjects, one patient had nausea and none had vomiting. As regards the effect of the injection on headache, in the group with migraine, the symptom was completely relieved in twelve of the fifteen experiments. In the control group, transient headache occurred in three of the twelve experiments (table 2, cases 7, 10 and 15).

*Cerebrospinal Fluid Pressure*—We have seen a report by only one author who has measured the spinal fluid pressure during an attack of migraine. In five cases Kerppola<sup>16</sup> found pressures of from 80 to 220 mm, with an average of 144 mm. In our nine cases in which readings of spinal fluid pressure were made during headache, the initial readings were 40 to 180 mm, with an average reading of 113 mm. For the group of fourteen patients used as controls, the initial pressures ranged from 95 to 175 mm, with an average of 130. If the two very

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<sup>16</sup> Kerppola, W. Ueber die Entstehung und Erweisbehandlung der Migräne. Monatschr f Psychiat u Neurol 61 83, 1926.



TABLE 1—*Effect of the Injection of Ergotamine Tartrate on the Pressure of the Spinal Fluid and of the Blood, on the Pulse Rate and on the Symptoms of Patients with Migraine Headache*

Case*	Dose of Ergot amine, Mg	Spinal Fluid Pressure, Mm Spinal Fluid		Radial Pulse Rate, Beats per Min		Arterial Pressure				Time in Minutes for Head ache to be		Nausea	Vomiting
		Basal Level	Average Change	Basal Level	Average Change	Systolic		Diastolic		Better	Gone		
						Basal Level	Average Change	Basal Level	Average Change				
1	0.25	40	+30	75	0	120	+ 5	80	0	(Not relieved)	0	0	
2a	0.50	110	- 5							(Not relieved)	0	0	
2b	0.50					130	+15	70	+25	(Not relieved)	+	+	
3a	0.50					120	+15	90	+10	16	61	+	+
3b	0.12	50	+25	110	- 5	110	+10	80	+10	32	56	+	+
4a	0.50	110	0							20	64	0	0
4b	0.15					155	+ 5	100	+10	11	43	0	0
4c	0.50					140	+30	90	+45	10	14	+	+
5	0.35	100	+15							30	33	+	0
6	0.50	180	+40	105	-15	140	+20	90	+15	25	30	0	0
7	0.25	145	+20							20	53	0	0
8	0.50	155	+15	110	-45	110	+15	70	+20	13	74	+	+
9	0.50	130	-25	75	- 5	100	+40	70	+10	40	72	+	+
10	0.25			70	- 5	100	+10	75	0	21	36	0	0
11	0.25					115	+ 5	70	+10	27	36	0	0
Average	0.38	113	+13	91	-13	122	+16	80	+14	22	48		

\* In cases 4b and 7, 0.12 and 0.25 mg of ergotamine was given subcutaneously at the same time as the intravenous injection. In cases 8, 10 and 11, 0.25 mg of ergotamine was given subcutaneously from twelve to sixty minutes after the intravenous injection.

TABLE 2—*Effect of Intravenous Injection of Saline Solution and of Ergotamine on the Pressure of the Blood and of the Spinal Fluid and on the Pulse Rate of the Control Series of Patients not Subject to Migraine*

Case	Dose of Ergotamine, Mg	Spinal Fluid Pressure, Mm Cerebrospinal Fluid		Radial Pulse Rate, Beats per Minute		Blood Pressure			
						Systolic		Diastolic	
		Basal Level	Average Change	Basal Level	Average Change	Basal Level	Average Change	Basal Level	Average Change
1	Saline solution	105	0	100	0	105	+5	70	+5
2	Saline solution	150	0	75	+2	140	-5	80	0
3	Saline solution	175	0	105	-5	120	-5	70	+5
4	Saline solution	110	0	100	+3	105	+5	65	+5
Average		135	0	95	0	118	0	71	+4
5	0.35	175	0	105	-20	115	+20	75	+15
6	0.35	160	+50	95	-15	120	+5	55	+15
7	0.50	110	+45	100	-15	100	0	55	+10
8	0.50	115	+35	100	0	130	+15	90	+5
9	0.50	110	0	85	-20	110	+5	75	+10
10	0.30	150	+35						
11	0.25	100	+30	75	-5	120	0	60	+5
12	0.50	105	+80	75	-10	125	+45	80	+20
13	0.45	145	+25	90	-10	110	+10	70	+20
14	0.50	95	+10						
15	0.50			110	-35	145	-15	65	+5
16	0.50			75	0	100	+15	70	+15
Average	0.43	127	+31	91	-13	118	+10	70	+12

low readings of 40 and 50 were eliminated from the values for the group with migraine, the average for the two groups would be the same.

As to the effects on the spinal fluid pressure of the injection of ergotamine, the only published observation on man is that made by Urechia<sup>17</sup>. Using the pressure apparatus of Claude, he observed a decrease of tension in eight patients and an increase in two. None of the patients was subject to migraine. The only report dealing with animals is that by Pool,<sup>18</sup> who gave injections to anesthetized cats of from one to ten times the clinical dose of ergotamine tartrate and observed either no change or a rise in the pressure of the spinal fluid.

Turning to the results obtained by us and shown in tables 1 and 2, after the administration of ergotamine the spinal fluid pressure of almost all the patients increased. The abrupt increase of spinal fluid pressure which occurred immediately after injection of ergotamine was undoubtedly due to the pain of the intravenous injection, since it occurred after the injection of saline solution as well as after the injection of ergotamine. After this transient rise, there was a secondary and prolonged rise in the two groups receiving an injection of ergotamine. The pressure remained constant after the first five minutes. As seen in table 1, of the nine patients subject to migraine who were given ergotamine in the midst of headache, only three did not exhibit a rise of spinal fluid pressure. For the other six, the increase in the general spinal fluid level for the period after the injection was from 15 to 40 mm. The average increase in the level of the pressure in the nine cases was 13 mm, or 11 per cent. In the group of ten patients not subject to migraine who were given ergotamine, none experienced a fall of pressure. The greatest rise in this group was 80 mm, the average increase in the pressure level was 31 mm, or 24 per cent (table 2).

In figure 1 is shown the time relation of the average pressure curve. The maximum elevation was reached seven minutes after injection in the group without migraine and sixteen minutes after injection in the group with migraine. The increase in spinal fluid pressure which followed the injection of ergotamine occurred later and was less pronounced in patients during an attack of migraine than in patients not subject to attack.

*Blood Pressure*—A number of investigators have reported the effect of ergotamine on the blood pressure of animals. Herrick<sup>19</sup> noted an

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17 Urechia, C. I., and Dragomir, L. L'influence du tartrate d'ergotamine, de l'adrénaline et de l'atropine sur la tension du liquide céphalo-rachidien, *Compt rend Soc de biol* **99**:1069, 1928.

18 Pool, J. L., and Nason, G. I. Cerebral Circulation. XXXV. The Comparative Effect of Ergotamine Tartrate on the Arteries of the Pia Dura and Skin of Cats, *Arch Neurol & Psychiat* **33**: 276 (Feb.) 1935.

19 Hewes, H. F., and Kendall, A. I. The Gas Bacillus as an Agent of Intestine Pressure in Femoral Artery of Dog, *Proc Soc Exper Biol & Med* **30**: 871 1933.

increase in the systemic blood pressure of anesthetized dogs, with a concomitant diminution of peripheral (limb) blood flow. Salant, Nadler and Brodman<sup>20</sup> reported an increase in one half and no change in the other half of a series of anesthetized cats. Marinesco<sup>21</sup> noted an increase in pressure after intravenous injection and a decrease after intraventricular administration of ergotamine. In a series of sixty-seven experiments on anesthetized cats given ergotamine tartrate intravenously, Pool<sup>18</sup> obtained an increase of blood pressure in 57 per cent. Rosen-

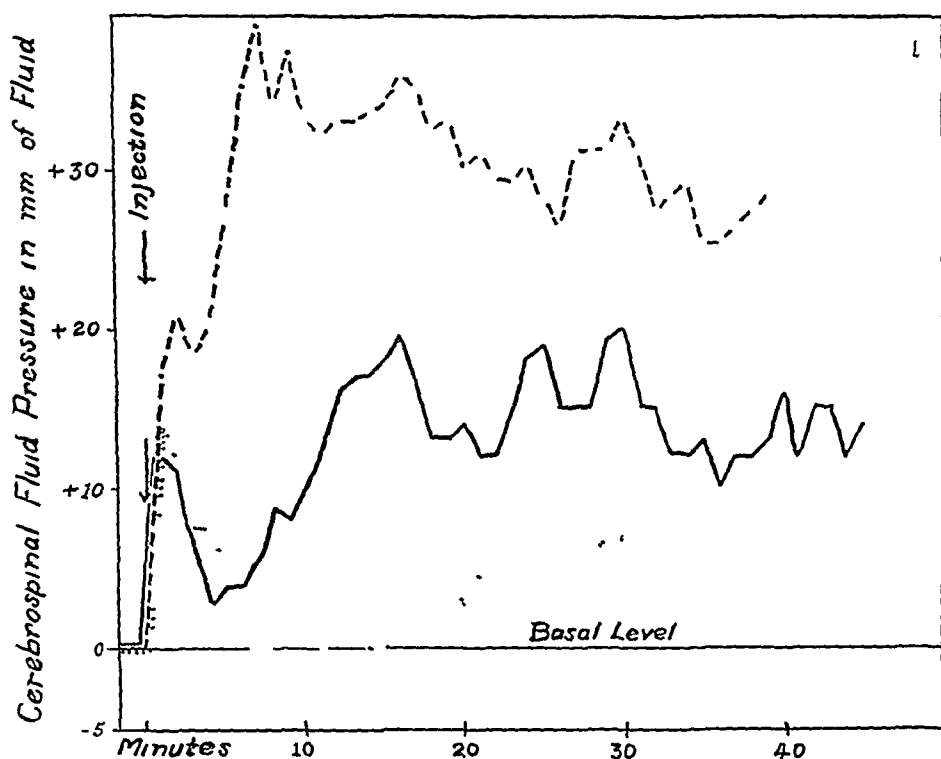


Fig 1—Changes in the spinal fluid pressure following the intravenous injection of from 0.25 to 0.5 mg of ergotamine tartrate. The curves represent the average of the mean readings for the group in question. The basal level is the spinal fluid pressure in the control period before injection. The ordinates represent increase or decrease of pressure (in millimeters of spinal fluid). The abscissas represent minutes of time. In order to represent the average pressure of all cases, the curves could be extended only as far as the shortest period of observation. The curves represent the nine patients having migraine headache, for whom the average amount of ergotamine injected was 0.38 mg (solid line), the control group of ten patients not subject to attacks, for whom the average amount injected was 0.4 mg (broken line), and the control group of four patients not subject to migraine headache, who were given 0.2 cc of saline solution (dotted line).

20 Salant, W., Nadler, J. E., and Brodman, K. Circulatory Reaction to Ergotamine and Effect upon Them Produced by Adrenalectomy and Blood  $pH$ , *Proc Soc Exper Biol & Med* **25** 361 (Feb) 1928.

21 Marinesco, G., Soger, O., and Kreindler, A. Action centrale de l'ergotamine sur la tension artérielle, *Compt rend Soc de biol* **107** 191, 1931.

blueth and Cannon<sup>22</sup> expressed the belief that the increase in blood pressure is due to a peripheral effect of the drug and the decrease to a central action. Wright<sup>23</sup> suggested that the rise in pressure may be due to abolition of the carotid sinus reflex. Experiments on animals show, therefore, that the intravenous injection of ergotamine tartrate produces a rise in systolic and diastolic blood pressure. These conclusions cannot be applied unreservedly to man because the animals were in most cases anesthetized and the doses were larger than the amounts used clinically.

Observations on man furnish more conflicting evidence. Barath<sup>24</sup> observed usually a fall in the systolic and a rise in the diastolic pressure. Elevation of the systolic pressure in patients with normal tension was observed by Immerwahr<sup>25</sup> and by Youmans and his associates<sup>26</sup> and in patients with hypertension by Immerwahr<sup>25</sup>. Depression of the systolic pressure was noted in patients with hypertension by Barath<sup>24</sup> and by Meakins and Scriver<sup>27</sup> and in patients with hypotension by Immerwahr<sup>25</sup>. These conflicting reports may be due, as suggested by Youmans and his associates,<sup>26</sup> to the condition of the patient, on the other hand, they may be due to the fact that some patients received the ergotamine intramuscularly or subcutaneously, while others received it by mouth.

Among the twenty-one observations of this study in which the blood pressure was recorded, the intravenous administration of ergotamine tartrate was followed by an increase of the systolic pressure in eighteen instances and by a decrease in one, in two there was no change. The average elevation was 13 mm of mercury, or 10 per cent. The diastolic pressure increased in nineteen cases and did not change in two. The average diastolic increase was 13 mm, or 17 per cent. Although the average pulse pressure did not change, there were distinct individual variations. The pulse pressure increased in eleven instances, decreased in eight and remained the same in two.

As regards the two groups, the patients with migraine and the controls, all of whom received ergotamine, each of the patients with

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22 Rosenblueth, A, and Cannon, W B. Some Circulatory Phenomena Disclosed by Ergotamine, *Am J Physiol* **105** 373, 1933.

23 Wright, S. Studies of Reflex Activity in Involuntary Nervous System. Action of Ergotamine on Vaso-Motor Reflexes, *J Physiol* **69** 331 (May) 1930.

24 Barath, E. Untersuchungen über die Ergotaminwirkung bei Menschen mit besonderer Rücksicht auf seine klinischen Anwendungsmöglichkeiten bei inneren Erkrankungen, *Ztschr f klin Med* **104** 713, 1926.

25 Immerwahr, P. Effects of Ergotamine on Pulse, Blood Pressure and Blood Sugar. Comparative Experiments with Atropine, *Med Klin* **23** 1693, 1927.

26 Youmans, J B, Trabue, C, and Buvinger, R S. Experimental and Clinical Studies of Ergotamine, *Ann Int Med* **7** 653 (Nov) 1933.

27 Meakins, J, and Scriver, W de M. Treatment [Ergotamine, Acetylcholine, Sodium, Thiocyanate] of Hypertension. *Canad M A J* **25** 285 (Sept) 1931.

migraine had an increase of systolic blood pressure of from 5 to 40 mm, the average increase in the general pressure level being 16 mm, or 12 per cent (table 1) Changes in the control group were more scattered,

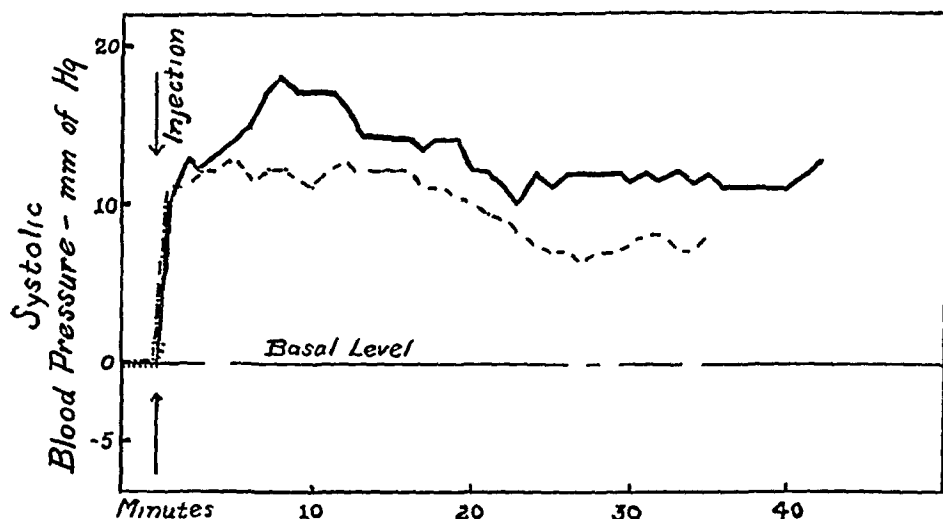


Fig 2—Changes in the systolic blood pressure following the intravenous injection of from 0.25 to 0.5 mg of ergotamine tartrate. The ordinates represent changes of blood pressure in millimeters of mercury, the abscissas, time in minutes. Other explanations are the same as those for figure 1, except that the numbers comprising the three groups are: patients having migraine headache, who were given ergotamine, eleven; patients not subject to attacks, who were given ergotamine, ten; and control patients, who were given saline solution, four.

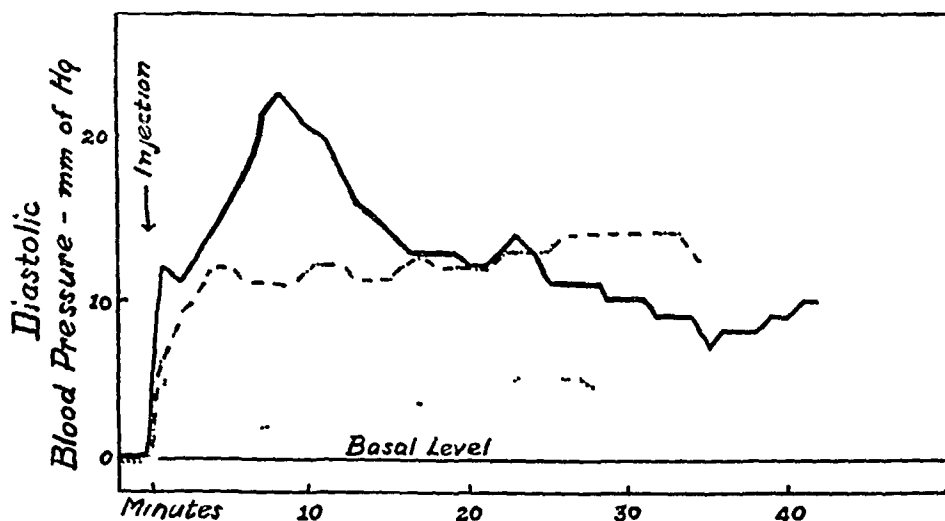


Fig 3—Changes in the diastolic blood pressure following the intravenous injection of from 0.25 to 0.5 mg of ergotamine tartrate. The explanations are the same as in figure 2.

from a decrease of 15 mm to an increase of 45 mm. The average maximum change was an increase of 10 mm, or 8 per cent (table 2). Inspection of figure 2 shows that the curves for blood pressure (in

contrast with the curves for spinal fluid pressure) had much the same form in the group with migraine as in the control group

In the case of the diastolic pressure, there was in both groups an average increase which approximated the increase in systolic pressure (tables 1 and 2) The curves, on the basis of time, as shown in figure 3, are, however, different In the group having migraine headache, there was a sharp increase of diastolic pressure in the first eight minutes after injection This was perhaps related to the nausea and vomiting which some of the patients experienced in this period

*Heart Rate*—Andrus and Martin<sup>8</sup> demonstrated that ergotamine tartrate slows the cardiac rate of animals, presumably by a depressant action on the cardiac sympathetic end-organs One of us (Pool<sup>18</sup>) observed that ergotamine given intravenously to anesthetized cats may

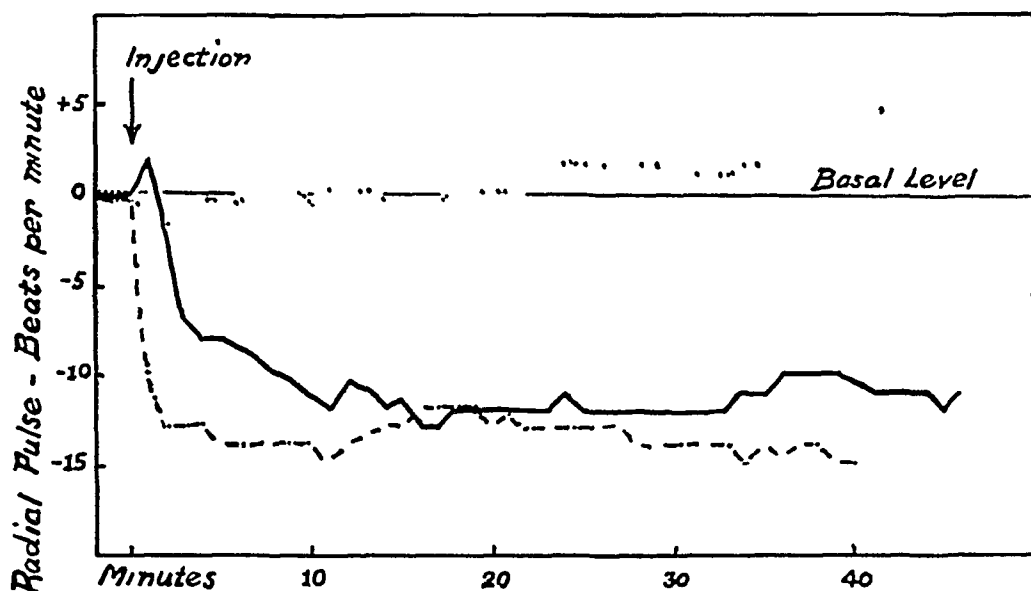


Fig 4—Changes in the pulse rate following the intravenous injection of from 0.25 to 0.5 mg of ergotamine tartrate The ordinates represent the pulse rate in beats per minute The abscissas represent minutes of time The number of patients in the three groups are patients with migraine headache who were given ergotamine, six, patients in the control group who were given ergotamine, ten, patients in the control group who were given saline solution, four

produce a marked slowing of the rate, occasionally with irregularity in rhythm

In man the cardiac rate is also slowed by the administration of ergotamine, as noted by Youmans and his associates,<sup>26</sup> who stated that the effect may be due to vagal excitation, and by Goldman<sup>28</sup> Porges,<sup>29</sup> Immerwahr,<sup>25</sup> Barath<sup>24</sup> and others In no report is an elevation of pulse rate mentioned The evidence presented in our study confirms these observations

28 Goldman, M Recherches cliniques sur l'action de l'ergotamine sur le système végétatif, Arch d mal du cœur 21:204, 1928

29 Porges, O Treatment of Hyperthyroidism Med Klin 23 200, 1927

The injection of ergotamine was followed by bradycardia in thirteen of the sixteen patients whose pulse rate was recorded. The average retardation throughout the postinjection period was from five to forty-five beats per minute. For the sixteen cases, the average decrease was thirteen beats, or 14 per cent. The degree of retardation was very slightly less in the group with migraine (tables 1 and 2). Inspection of figure 4 shows that during the first ten minutes bradycardia was less in the group with migraine. Here again the frequency of vomiting in this group may be explanatory.

#### COMMENT

What is the significance of the foregoing observations? Can the observed changes in pressure or circulation, consequent to the administration of ergotamine, explain its beneficial effect?

In regard to measurements of intracranial pressure, a finding of subnormal pressure during the attack of migraine would suggest a constriction of the cerebral vascular bed or dehydration of cerebral tissues. In our observations, however, the initial spinal fluid pressure, except in two instances, was not abnormally low, nor did the time of relief from headache in patients coincide with the period of increasing pressure. Furthermore, control patients without headache and patients who were not relieved of headache had as great or a greater rise than patients who were relieved. Two patients who were relieved had a decrease in pressure. These facts permit us to conclude that changes in pressure per se explain neither the presence nor the relief of headache. The observations on pressure do not, however, justify a similar statement concerning a possible generalized vascular spasm. Acute changes in the caliber of cerebral vessels are promptly reflected in increase or decrease of the spinal fluid pressure, but established vascular changes may not be.

If there were spasm of cerebral vessels, the headache might be explained either by a resultant stimulation of sensory nerves or by defective oxygenation or nutrition of tissues. In the latter case, the good effect of ergotamine could be attributed to an improved cerebral blood flow, with flushing away of toxic substances or improvement of the oxygenation of cerebral tissues. Headache is a common symptom of chronic anoxemia. As a matter of fact, Lennox and Gibbs<sup>30</sup> found that ergotamine tartrate does increase the cerebral blood flow in both patients subject to and those not subject to migraine. As in the case of intracranial pressure, the observed improvement in cerebral blood flow cannot be the whole cause of the relief of headache, for other drugs, such as

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30 Lennox, W. G., Gibbs, E. L., and Gibbs, F. A. The Cerebral Circulation. XXXVI. Effect of Ergotamine Tartrate on the Cerebral Circulation of Man, *J. Pharmacol. & Exper. Therap.* **53**: 113 (Jan.) 1935.

epinephrine, histamine and carbon dioxide (inhaled), which give an even greater increase in flow, do not have the same dramatic effect on headache

The observed increase in cerebral blood flow after administration of ergotamine is probably secondary to the increase in blood pressure. Neither the increase in blood pressure nor the decrease in pulse rate was significantly different in the patients with migraine and the controls. The only difference which seems important is the relatively small increase in spinal fluid pressure in patients during headache. This cannot be explained by differences in blood pressure, for the group with migraine had a slightly greater increase in blood pressure. Is it possible that the cerebral vessels of patients having headache dilate less readily after injection of ergotamine than the vessels of patients not subject to migraine?

But does ergotamine dilate cerebral vessels? The evidence of increased intracranial pressure is too indirect, for other things might cause the increase. Direct evidence is not supportive. Pool<sup>18</sup> did not obtain a consistent response in pial arterioles of the cat. Nor did Lennox and Gibbs<sup>30</sup> find a sufficient increase in the cerebral blood flow in patients to indicate dilatation of cerebral arterioles. One may conclude that these observations do not indicate that either abnormalities in intracranial pressure (generalized cerebral vascular spasm) or abnormalities in the speed of cerebral blood flow are of specific or exclusive importance in the production or in the relief of migraine headache.

The possibility remains that there may be localized vascular or pressure changes within the cranial cavity which are responsible for pain and which are not reflected in the gross measurements which we have made. Various authors (Hare,<sup>31</sup> Cushing,<sup>32</sup> Dickerson<sup>33</sup> and others) have contended that the pain of migraine arises not from cerebral but from dural arteries. Dickerson secured relief in a small series of cases by ligation of the middle meningeal artery or arteries. Pickering,<sup>34</sup> on the basis of observations of the blood pressure and the spinal fluid pressure after intravenous injection of histamine, stated the belief that the pain of this procedure is due to perivascular edema of dural vessels with pressure on sensory nerves. Most important for our purposes is

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31 Hare, F. The Mechanism of Pain in Migraine, *M. Press & Circ.* **79** 583, 1905

32 Cushing, H., in Keen, W. W. *Surgery Its Principles and Practice* Philadelphia, W. B. Saunders Company, 1908, vol. 3, p. 160

33 Dickerson, D. G. Surgical Relief of the Headache of Migraine, *J. Nerv. & Ment. Dis.* **77** 42, 1933

34 Pickering, G. W. Observations on the Mechanism of Headache Produced by Histamine, *Clin. Sc.* **1** 77 (July) 1933



the observation made by Pool<sup>35</sup> that in cats dural vessels consistently respond to injection of ergotamine by constriction (as do vessels of the skin), an action dissimilar to that of pial or cerebral vessels. Conceivably, constriction of dilated and engorged dural vessels might explain the relatively small increase in spinal fluid pressure of patients having migraine who are given ergotamine.

In the group of patients whose headaches were relieved by ergotamine, the average period after intravenous injection before relief began was twenty-two minutes, and before the pain disappeared, forty-eight minutes. A glance at the charts will show that the changes in the pressure of the spinal fluid and of the blood and in the pulse rate occurred much more quickly, usually within ten minutes after injection. It seems probable that any explanation of the mechanism of the relief of pain by ergotamine would be a complicated one and include alterations in the vascular bed and blood flow and in dynamics and fluid balance. In this event the few physiologic changes which we have observed would be of contributory importance.

In place of, or in addition to, these considerations, it is possible that ergotamine acts directly as a sedative on the sensory nerves which supply intracranial tissues, particularly those nerves which accompany arteries or supply the dura, or that it acts directly on autonomic nuclei in the hypothalamus. Such a simple explanation does not, however, take into account the fact that ergotamine relieves not only the headache but also other symptoms, such as scotoma, hemianopsia, paralysis and malaise. Obviously the whole problem requires further study.

#### CONCLUSIONS

With patients subject to migraine and control patients not subject to the disease, observations have been made on the effect of intravenous injection of ergotamine tartrate on the pressure of the spinal fluid and of the blood, on the pulse rate and on the clinical symptoms. In fifteen experiments the patient was in the midst of a migraine headache. In sixteen, the patient was not subject to migraine, and in four of these, saline solution was injected in place of ergotamine.

The average initial spinal fluid pressure during headache was 113 mm, a figure 14 mm lower than the average pressure for the control group.

Following the injection of ergotamine, there was in both groups a prompt fall in pulse rate and a rise in systolic and diastolic blood pressure and in spinal fluid pressure.

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35 Pool, J. L., Mason, G. I., and Forbes, H. S. The Cerebral Circulation XXXIII. The Effect of Nerve Stimulation and Various Drugs on the Vessels of the Dura Mater, *Arch. Neurol. & Psychiat.* **32** 1202 (Dec.) 1934.

After injection of ergotamine in the patients having headache, the average rise in the level of spinal fluid pressure was 13 mm , in the controls the level rose 31 mm

The relief from headache which twelve of the fifteen patients with migraine experienced could not be directly or entirely explained by the observed changes in cerebrospinal fluid pressure or in the circulation. The observations do not lend support to the theory that in migraine headache there is a generalized spasm of cerebral vessels or an abnormality of intracranial pressure.

# CHEMICAL STUDIES OF ACUTE POISONING FROM MERCURY BICHLORIDE

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## I ELIMINATION OF MERCURY DURING TREATMENT

The outcome of acute poisoning with mercury bichloride depends chiefly on the amount of mercury absorbed. Prompt emesis is therefore the most efficient treatment<sup>1</sup>. This should be supplemented as soon as possible with copious gastric lavage. Further elimination of the mercury has been sought by repeating the gastric lavage through the subsequent days, by extensive colonic irrigations and by pushing the consumption of fluids to secure diuresis. Local cleansing is a part of the therapeutic intent, but the expected removal of mercury generally has a large share in inciting the prescribing of these measures. As there are apparently no data on how effectively this object is accomplished and on how much mercury is really removed by such treatment, it appeared worth while to undertake these studies. They include the quantitative determination of mercury, by the method described by Booth<sup>2</sup> and ourselves, in the vomitus obtainable, in all the return fluids of gastric lavage and colonic irrigation, in the feces, both those passed in spontaneous stools and after enemas, and in the urine of four patients with acute poisoning from mercury bichloride. The selection proved fortunate, as in two cases the condition was fatal and in the other two it was very mild. The medical service of the university hospitals contributed the material. The patients were brought to the hospital between one-half and one and a half hours after taking from 2 to 25 tablets (0.5 Gm. each) of mercury bichloride, generally in solution. All had vomited before they came to the hospital, in only one case was a specimen of the early vomitus obtained for analysis, and this was incomplete. The quantity of mercury bichloride remaining when the patient came to treatment is therefore unknown. On admission the patients

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This work was aided by a grant from the Therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association

1 Goldblatt, Samuel. Acute Mercurial Intoxication, *Am J M Sc* **176** 645, 1928

2 Schreiber, N. E., Sollmann, T., and Booth, H. S. The Determination of Traces of Mercury, *J Am Chem Soc* **50** 1620, 1928

were treated according to the usual routine of the hospital. The stomach was washed with several liters of diluted (4 or 5 per cent) solution of sodium bicarbonate, this was repeated at intervals. Vomiting continued more or less in several cases. Copious colonic lavage with physiologic solution of sodium chloride was started on the same day and

TABLE 1—*Mercury Recovered from Emesis and Gastric Lavage*

Time	Emesis		Gastric Lavage	
	Volume, Cc	Mercury, Mg	Volume, Cc	Mercury, Mg
W W S About 9 Gm of mercury bichloride taken 4/5/32 at 6 00 p m				
4/ 5/32 7 00-11 00 p m	200	30 36	3,500	35 07
	200	8 8	3,220	21 91
	220	6 4	3,220	0 97
11 00 p m	170	0 61	2,500	6 5
Total for the first five hours		46 17		64 45
4/ 6/32 2 00 a m	100	0 1		
3 00 a m	100	0 24		
9 00 a m			3,030	0 09
9 00 p m	35	0 19		
Total for the second day		0 53		0 09
4/ 7/32	100	0 19	2,350	0 19
4/ 8/32	75	0 03		
Total		46 92		64 73
L R O About 5 5 Gm of mercury bichloride taken 3/14/33 at about 9 00 a m				
3/14/33 10 00 a m	150	159 1		
10 15 to 10 45 a m			2,820	28 48
6 00 p m	10	1 36		
Total		160 46		28 48
C B N About 2 5 Gm of mercury bichloride taken 11/2/32 at 9 15 a m				
11/ 2/32 Before lavage	75	39 6		
			5,500	24 75
2 00 p m			3,400	1 02
6 00 p m			3,820	0 23
11/ 3/32 1 00 a m			3,450	1 82
4 00 p m			1,700	0 14
Total		39 6		27 96
M C N About 1 Gm of mercury bichloride taken 3/7/32 at 10 00 p m				
3/ 7/32 10 20 p m				10 00*
3/ 8/32 7 30 a m	80	0 03		
3 00 p m			2,100	0 168
6 30 p m			2,300	0 046
3/11/32	70	0 0		
Total		0 03		10 214*

\* Specimen of 180 cc contained 0 61 mg of mercury (0 34 mg per hundred cubic centimeters), assuming that 3 liters was used, the amount recovered equals 10 mg of mercury

repeated, generally three times a day, until the end. In the two fatal cases anuria promptly developed, and the patients died after from five to nine days of nephritis and consequent pulmonary edema. Both had severe gastro-enteritis. The patients with mild poisoning did not have oliguria and showed few symptoms after the first day. They were discharged as well on the fifth and eighth day, respectively. Brief accounts of the histories of the individual patients follow. These are arranged in the order of severity of the poisoning. The time and

number of gastric and colonic irrigations are shown with the analytic data in tables 1 and 2. Symptoms and treatments that are not especially relevant to the present inquiry are omitted.

TABLE 2—*Elimination of Mercury in Stools, Both Spontaneous and After Enemas, and Colonic Irrigations*

		Stools*		Colonic Irrigations	
Time		Volume, Cc	Total Amount of Mercury, Mg	Volume, Cc	Total Amount of Mercury, Mg
W W S	About 9 Gm of mercury bichloride taken 4/5/32 at 6 00 p m				
4/ 5/32	Before 11 00 p m	800	3 60	3,400	0 48
		270	34 54	4,050	0 77
		285	13 10		
	11 30 p m	600	2 38		
	Midnight	250	18 2		
4/ 6/32	2 00 a m	75	1 46		
	4 00 a m	200	4 36		
	8 00 a m			4,960	1 29
	9 45 a m	225	0 23		
	1 00 p m	250	0 65		
	4 00 p m	50	1 28	3,470	0 28
	Midnight			3,150	0 28
4/ 7/32	8 00 a m }			2,960	0 24
	4 00 p m }	100	3 02	2,750	0 14
	Midnight }			2,500	0 75
4/ 8/32	8 00 a m }			3,230	0 19
	4 00 p m }	30	1 34	2,600	0 52
	Midnight }			2,875	0 11
4/ 9/32	8 00 a m }			3,350	0 30
	4 00 p m }	180	5 44	3,550	0 28
	Midnight }			2,500	0 15
4/10/32	8 00 a m }			3,100	1 8
	4 00 p m }	50	1 36	1,500	1 43
Total			91 0		9 0
L R O	About 5 5 Gm of mercury bichloride taken 3/14/33 at about 9 00 a m				
3/14/33	1 00 p m		7 9		
	6 00 p m			6,750	1 35
	7 00 and 9 00 p m	10	0 39		
3/15/33	9 00 a m	E 250	0 79		
	7 00 p m	200	2 36		
3/16/33	9 30 a m	E 920	0 65		
	5 00 p m	300	2 22		
3/17/33		E 740	0 09		
		1,000	3 55		
3/18/33		E 1,000	0 09		
		2,000	2 05		
3/19/33		E 450	0 16		
		400	0 39		
3/20/33		E 800	1 06		
		650	1 35		
3/21/34		E 100	0 04		
		150	0 34		
3/22/23		E 200	0 06		
Total			23 5		1 4
C B N	About 2 5 Gm of mercury bichloride taken 11/2/32 at 9 15 a m				
11/ 2/32		300	0 45	3,850	1 73
		225	3 80	3,850	0 73
		300	0 82	3,850	0 81
11/ 3/32	9 00 a m			7,450	0 30
	4 00 p m			4,300	0 25
	7 00 p m	300	0 18		
11/ 4/32	11 30 a m			7,450	0 15
	4 00 a m			7,400	0 15
Total			5 25		4 12

\* E indicates enema

TABLE 2—*Elimination of Mercury in Stools, Both Spontaneous and After Enemas, and Colonic Irrigations—Continued*

		Stools*		Colonic Irrigations	
Time		Volume, Cc	Total Amount of Mercury, Mg	Volume, Cc	Total Amount of Mercury, Mg
M C N	About 1 Gm of mercury bichloride taken 3/7/32 at 10 00 p m				
3/ 8/32	Midnight	E 930	1 42		
	2 30 a m	E 1,030	2 96		
	3 00 a m			4,440	1 73
	7 00 a m			5,620	0 17
	2 00 p m			3,000	0 06
	7 00 p m	75	1 72		
3/ 9/32	8 00 a m	1,500	1 25	3,820	0 11
	4 00 p m			3,770	0 11
	6 00 p m	110	0 14		
3/10/32	8 00 a m			5,220	0 0
	4 00 p m			5,600	0 05
3/11/32	8 00 a m			6,000	0 12
	4 00 p m			5,800	0 06
3/12/32	8 00 a m			5,800	0 12
	4 00 p m			5,800	0 64
Total			7 59	Mixed with feces	3 17

#### REPORT OF CASES

CASE 1—On April 5, 1932, about 6 p m, W W S, a Negress aged 25, dissolved 25 tablets (0.5 Gm each) of mercury bichloride in water and drank between a half and the whole of this (about 9 Gm of mercury bichloride) according to varying reports. The patient had not taken any food for the preceding eight hours. She vomited within three or four minutes and was treated in twenty minutes with apomorphine hydrochloride,  $\frac{1}{10}$  grain (64 mg) hypodermically, and with the whites of three eggs in a quart (946 cc) of milk. Almost continuous vomiting set in within a few minutes. The patient was admitted to the emergency ward at 7 p m and was given gastric lavage and treated for shock. She vomited repeatedly during the remainder of the first day and several times on the second and third days. The stools were bloody. Gastric lavage with 3 or 4 liters of solution of sodium bicarbonate was given at intervals during three days. Colonic irrigations with 0.8 per cent solution of sodium bicarbonate were given three times a day until death. Anuria persisted throughout. Death from respiratory failure occurred on the fifth day. Permission for autopsy was refused.

CASE 2—On March 14, 1933, about 9 a m, L R O, a white man 49 years old, swallowed 11 (0.5 Gm each) tablets of mercury bichloride. He vomited before admission (accounts were discordant as to amount and time). Part of the vomitus expelled at 10 a m was analyzed. The patient was admitted to the emergency ward at 10 15. The stomach was lavaged with 5 per cent solution of sodium bicarbonate. He vomited repeatedly on the first day, but only partial specimens were analyzed. Bloody diarrhea developed several hours after his admission. Colonic irrigations with 7 liters of physiologic solution of sodium chloride were given at 6 p m on the first day, and enemas were administered daily until death. Complete anuria continued from 5 p m of the first day until the fifth day, then oliguria persisted until death (catheterization gave 50 cc of fluid on the sixth day, 180 cc on the seventh day and 270 cc on the eighth day). Marked edema and anasarca developed, and the patient died of pulmonary edema. Autopsy showed gastro-enteritis, colitis and nephritis.

CASE 3—On Nov 2, 1932, about 9 15 a m, C B N, a Negress 32 years old swallowed 5 tablets (0.5 Gm each) of mercury bichloride (total dose 2.5 Gm).

in coffee. She vomited in ten or fifteen minutes and was admitted to the emergency ward at 9 45 a m. Gastric lavage with 6 liters of solution of sodium bicarbonate was administered. Further lavage was given at 2 and at 6 p m on this day and twice on the next day. Repeated colonic irrigations were administered. Polyuria occurred from forced intake of fluids. The patient felt well on the next day.

CASE 4—On March 7, 1932, at about 9 55 p m, M C N, a white woman aged 40, swallowed 2 tablets (0.5 Gm each) of mercury bichloride (total dose, 1 Gm). She vomited in five and ten minutes, the specimens were not analyzed. She was admitted to the emergency ward between 10 20 and 10 35 p m. Gastric lavage was given and repeated twice on the next day. Only part of the material recovered was saved for analysis. Colonic irrigation with solution of sodium bicarbonate was given three times on the first day and twice daily until the patient was discharged. The volume of urine was above normal throughout.

#### QUANTITATIVE DATA ON THE ELIMINATION OF MERCURY

In view of the paucity or absence of published data on the removal of mercury by lavage in cases of acute mercury poisoning, it seems advisable to record the results of analysis rather fully.

*Emesis After Patients Came Under Observation*—All the patients reported on here had vomited before they came to the hospital. There is little information as to how much mercury bichloride was lost this way, but presumably it was the greater part of the amount taken. In one case (that of L R O) a specimen was preserved, and this fraction contained 159 mg of mercury, about 37 per cent of the amount taken. After the patient's admission the mercury eliminated by emesis was insignificant in all instances, namely, 46.2, 1.36, 39.6 and 0.03 mg of mercury, equivalent to 0.7, 0.03, 2.1 and 0.004 per cent of the amount taken.<sup>3</sup> Practically all of this was found in the first vomitus after admission, as shown in table 1. Prolongation of emesis is therefore of no value for the elimination of mercury.

*Gastric Lavage*—Promptly after admission, i e, in from one-half to one and a half hours after the poison was swallowed, the stomach was washed with from 3 to 5 liters of 4 to 5 per cent solution of sodium bicarbonate, and the lavage was usually repeated several times in the first day, in one case it was repeated at varying periods on two subsequent days, as shown in table 1. The total amount of mercury removed by lavage amounted to 64.7, 28.5, 28 and 10.2 mg of mercury, equivalent to 0.95, 0.7, 1.51 and 1.37 per cent of the amount taken. These quantities are also rather insignificant. Practically all the mercury that was obtainable by gastric lavage was secured in the first washing in the emergency room, the later washings in the ward containing only

<sup>3</sup> The cases are always arranged in order of decreasing severity 1 to 4, WWS, LRO, CBN and MCN.

0.75, 3.21 and 0.21 mg. The first gastric lavage is of course imperative, the later repetitions appear to be of little value for the removal of mercury.

*Elimination Through Intestines*—The stools and material recovered after irrigations of the colon would contain any mercury which had escaped absorption after passing the pylorus and mercury which had been excreted with the bile and through the intestines. The presence of severe colitis has perhaps helped to give the impression that these quantities would be considerable, so that they would be toxic locally and perhaps systemically by reabsorption. This is partly responsible for the emphasis on colonic irrigation. The facts as shown in table 2 are instructive. The total amount of mercury which passed through the rectum during the entire stay of the patients in the hospital was as follows (in milligrams)

	Case			
	1	2	3	4
Stools, spontaneous and after enemas	90.94	23.49	5.25	7.59
Colonic irrigations	9.01	1.35	4.12	3.17
Totals	99.95	24.84	9.37	10.76
Percentage of dose	0.65	0.61	0.50	1.45
Days	5	9	3	5

The absolute amount as well as the percentage is surprisingly small, so evidently the mercury that passes from the stomach into the intestine is effectively absorbed and little is reexcreted by this channel. This excretion is not increased by colonic irrigations, which in the whole period generally contained less than 4 and never more than 9 mg. of mercury. The irrigations may be useful in combating colitis but not for the removal of mercury. The elimination of mercury from the intestines is greatest on the first day, it falls to from one third to one twelfth on the second day and then runs an irregular course, about one half of the level of the second day being eliminated each day for the remainder of the period of observation averaging as follows:

Patient	Time	Average Intestinal Elimination of Mercury per Day (Mg.)
W. W. S.	Third to fifth day	4.70
L. R. O.	Third to ninth day	1.72
C. B. N.	Third day	0.30
M. C. N.	Third to fifth day	0.33

The late elimination from the intestines, therefore, varies with the dose. It probably represents excreted rather than unabsorbed mercury.

*Urine*—This is shown in table 3. The most severely poisoned patient, W. W. S., was anuric throughout, consequently there was no urinary excretion of mercury. The other fatally poisoned patient eliminated nearly 10 mg. of mercury in the first eight hours, a high level for the urine but a very small amount in relation to the dose. This patient then became anuric. In the fatal cases, therefore, little or no mercury was eliminated in the urine. The two mildly poisoned patients



had marked polyuria, due to forcing of the intake of fluids and perhaps also to the diuretic effect of the smaller doses of mercury. Notwithstanding the polyuria, the kidneys excreted only small quantities of mercury, totaling 1.5 and 2.3 mg in the five days and averaging from 0.3 to 0.5 mg per day. Even on the first day, the excretion was only 1 and 1.7 mg. The excretion of mercury in the urine, therefore, seems insignificant in acute mercuric poisoning, even when the patient is polyuric.

TABLE 3—*Elimination of Mercury in the Urine*

	Volume of Urine, Cc	Total Amount of Mercury, Mg
W W S About 9 Gm of mercury bichloride taken 4/5/32 at 6 00 p m , anuria until death on the fifth day		
L R O About 5.5 Gm of mercury bichloride taken 3/14/33 at 9 a m First eight hours	600	9.7
Anuria until the sixth day, then small quantities by catheter (50 cc on sixth day, 180 cc on seventh day, 270 cc on eighth day), mercury not reported, but amount would have been insignificant		
C B N About 2.5 Gm of mercury bichloride taken 11/2/32, 9 15 a m		
11/ 2/32 11 30 a m (on admission)	250	0.58
4 00 p m	200	0.21
6 00 p m	350	0.04
6 00 p m to 11 00 p m	450	0.05
11 00 p m to 7 00 a m	1,600	0.06
Total for 32 hours		0.97
11/3 to 11/4, 7 00 a m to 7 00 a m	6,640	0.27
11/4 to 11/5, 7 00 a m to 7 00 a m	5,350	0.05
11/5 to 11/6, 7 00 a m to 7 00 a m	3,600	0.11
11/6 to 11/7, 7 00 a m to 7 00 a m	1,900	0.10
Total in five days		1.5
M C N 1 Gm of mercury bichloride taken 3/7/32, 9 55 p m		
3/ 8/32 7 00 a m	170	0.74
11 00 a m	290	0.41
1 45 p m	720	0.49
7 00 p m	900	0.07
Total for nineteen hours		1.71
3/ 9 to 3/10, 7 00 a m to 7 00 a m	2,110	0.21
3/10 to 3/11, 7 00 a m to 7 00 a m	1,860	0.13
3/11 to 3/12, 7 00 a m to 7 00 a m	1,400	0.13
3/12 to 3/13, 7 00 a m to 7 00 a m	800	0.12
Total for five days		2.30

*Summary*—The relative rôle of the various channels of elimination and treatments is shown in table 4. The first two divisions give the amounts eliminated during the whole sojourn in the hospital. Emesis was not included since complete data were not available. It is seen that the total quantities of mercury removed by gastric and colonic lavage in the stools and in the urine during this entire period are only from 0.5 to 3 per cent of the total amounts. The actual amounts ranged from 2.3 to 16.4 mg of mercury. The fatal dose of absorbed mercury

bichloride is not known. If in analogy to experiments on animals 5 mg per kilogram is taken as a fair approximation, this would amount to 300 mg of mercury per person. On this basis, the amount eliminated, except for emesis, would represent from one tenth to one half of the fatal dose. Practically all of this was in the gastric lavage of the first day and in the feces. Copious, prolonged colonic irrigations removed in all instances from one two hundredths to one thirty fifth of this assumed fatal dose, and up to one thirtieth of the dose was excreted in the urine.

TABLE 4—*Total Amount of Mercury Removed*

Patients		W W S	L R O	C B N	M C N
Dose of mercury bichloride		9.0 Gm	5.5 Gm	2.5 Gm	1.0 Gm
Mercury equivalent		6.6 Gm	4.06 Gm	1.85 Gm	0.74 Gm
Milligrams of mercury recovered	Gastric lavage	64.7	28.5	28.0	10.2
	Feces, spontaneous and after enemas	91.0	23.5	5.25	7.59
	Colonic irrigations	9.0	1.4	4.12	3.17
	Urine	0.0	9.7	1.5	2.3
	Total	164.7	63.1	38.9	23.26
Percentage of amount taken	Gastric lavage	0.98	0.70	1.51	1.37
	Feces, spontaneous and after enemas	1.38	0.58	0.28	1.02
	Colonic irrigations	0.13	0.034	0.22	0.42
	Urine	0.0	0.23	0.08	0.31
	Total	2.49	1.54	2.09	3.12
		From 6 Hours to 6 Days	From 12 Hours to 9 Days	From 15 Hours to 5 Days	From 22 Hours to 6 Days
Mercury (Mg) removed by					
Emesis		0.75	0.0	0.0	0.0
Gastric lavage		0.28		1.96	
Feces, spontaneous and after enemas		19.14	15.20	0.18	1.98
Colonic irrigations		7.75		0.85	0.60
Urine				0.59	0.59
Total		27.92	15.20	3.58	3.17

## CONCENTRATION OF MERCURY IN EXCRETA

The concentration of mercury in the vomitus, stools and urine helps to decide whether the mercury in the digestive tract is unabsorbed or excreted and also throws light on the possibility of local injury by the excretion of mercury. The concentration in the specimens of vomitus and feces is cited only when there was no gastric lavage or colonic irrigation, respectively, for several hours preceding the collection. The data are shown in table 5. The concentrations always refer to milligrams per hundred cubic centimeters or parts per hundred thousand.

*Vomitus*—The two highest concentrations, 53 and 106 mg of mercury per hundred cubic centimeters, are for emesis within the first hour, before lavage. One patient, L. R. O., who was given relatively little lavage still yielded 13.6 mg per hundred cubic centimeters at the

end of nine hours All the others yielded less than 1 mg per hundred cubic centimeters, ranging from 0.04 to 0.34 mg, between eight and twenty-seven hours, and the average concentration was 0.19 mg on the second day and 0.04 mg on the third day The low concentration suggests that this represents excreted rather than unabsorbed mercury

*Feces*—The concentration in the stools was distinctly higher than that in the late samples of vomitus but naturally lower than in the early

TABLE 5—*Concentration of Mercury (Milligrams per Hundred Cubic Centimeters) in the Excreta*

Patient	Dose of Mercury Bichloride	Vomitus		Stools		Urine	
		Time*	Concentration	Time	Concentration	Time	Concentration
W W S	9 Gm	8 hours 9 hours 27 hours 2nd day 3rd day	0.10 0.24 0.34 0.19 0.04	First 12 hours  2nd day 3rd day 4th day 5th day	0.4 to 12.8 median 2.9  0.28 to 3.02 4.50 3.00 2.72	Anuria	
L R O	5.5 Gm	1 hour 9 hours	106.0† 13.6	Diarrhea 12 hours 2nd day 3rd day 4th day 5th day 6th day 7th day 8th day	3.90 1.20 0.74 0.36 0.11 0.10 0.20 0.23	8 hours	1.620
						Anuria after eight hours	
C B N	2.5 Gm	½ hour	53.2†	1st day  2nd day	0.15 1.70 0.27 0.08	2 hours 7 hours 9 hours 14 hours 22 hours 2nd day 3rd day 4th day 5th day	0.230 0.110 0.010 0.020 0.004 0.004 0.001 0.003 0.005
M C N	1 Gm	10 hours	0.04	21 hours 2nd day	2.30 0.09 0.13	9 hours 13 hours 16 hours 21 hours 2nd day 3rd day 4th day 5th day	0.450 0.140 0.070 0.008 0.010 0.007 0.009 0.015

\* The time is that which elapsed after the taking of the poison

† Concentration of mercury before first lavage

samples The highest concentration of mercury in the stools was for the most severely poisoned patient, W W S, it reached 12.8 mg per hundred cubic centimeters on the first day and ranged between 2.7 and 4.5 mg on the last three days before death The failure of the concentration to decline after the first day indicates the presence of excreted rather than unabsorbed mercury The other fatally poisoned patient, L R O, had diarrhea until death, and the fecal concentration of mercury was accordingly lower, progressing from 3.9 mg per hundred cubic centimeters on the first day to 0.36 mg on the fourth day From then until death, on the eighth day, it oscillated between 0.1 and 0.23 mg

This continued level presumably represents excretion. The two patients with mild poisoning attained values of only 1.7 and 2.3 mg of mercury per hundred cubic centimeters on the first day, and the amounts fell to 0.06, 0.09 and 0.13 mg on the second day. It appears from the persistence of the concentration in late specimens that the amount of mercury in the feces after the second or third day represents excreted rather than unabsorbed mercury. The level maintained in the case of most severe poisoning, from 2 to 4 mg per hundred cubic centimeters, could be conceived as injurious. The values in the other cases, from 0.15 to 0.23 mg, fall within the range of values for the concentration in urine found in cases in which mercury has been administered therapeutically and would therefore probably not be locally injurious.

*Urine*—The concentration of mercury in the urine could not be estimated in the fatal cases because of anuria. In the cases of mild poisoning it is very low (partly because of polyuria), 0.27 and 0.45 mg per hundred cubic centimeters even on the first day and only from 0.001 to 0.015 mg after the first day. These concentrations are lower than those often found in patients given mercurial therapy and are therefore not injurious to the urinary organs. The concentration found in the early samples of urine of the fatally poisoned patient, L. R. O., 1.62 mg per hundred cubic centimeters, would presumably be injurious.

*Summary*—For the three excreta the range and the median of the concentrations for all the patients are (mg per hundred cubic centimeters)

	Range	Median
Vomit	0.03 to 106.1	0.24
Feces	0.06 to 12.8	0.74
Urine	0.001 to 1.62	0.01

For the individual patients, the medians (exclusive of the early samples of vomit of L. R. O.) are

Patient	Vomit	Feces	Urine
W. W. S.	0.19	2.6	
L. R. O.	13.6	0.30	
C. B. N.		0.21	0.005
M. C. N.		0.13	0.012

It is seen that the concentration in the feces was from eleven to forty times that in the urine for C. B. N. and M. C. N. and fourteen times higher than that in the vomit for W. W. S. The vomit of L. R. O. alone had a higher concentration than the feces, but it evidently represented unabsorbed, not excreted, mercury. It appears, then, that mercury is eliminated in considerably higher concentration from the intestinal tract than from the stomach or in the urine. Very likely the relatively high intestinal concentration occurs in the bile, although the

excretion of granular mercurial compounds by the intestinal lymphocytes may play a part

#### SUMMARY AND CONCLUSIONS

The elimination of mercury was studied in four cases of acute corrosive poisoning from mercury bichloride, two fatal and two mild, in which the patients were treated by copious gastric lavage and colonic irrigations

Only the early emesis removed considerable quantities of mercury. The total amount removed by gastric lavage and colonic irrigations and in the stools and urine amounted to only from 23 to 164 mg of mercury, representing from 1.5 to 3.25 per cent of the mercury taken. Initial gastric lavage is imperative, but later repetition is superfluous. Colonic irrigations removed only insignificant quantities, from 1.4 to 9 mg of mercury. The urinary elimination was also almost negligible, in the cases of severe poisoning there was anuria. In those of mild poisoning there was polyuria but the total urinary excretion of mercury in five days was only 1.5 and 2.3 mg.

The concentration of mercury after the first, second or third day ran practically level in the vomitus, feces and urine, indicating that the mercury in the stomach and intestines at this time is being excreted. The concentration was ten times higher or more in the feces than in the urine or the late vomitus. In general, the concentrations, even in the feces, were within the limits of the concentration found in the urine in cases of the therapeutic use of mercury and would therefore not be materially irritant. The fecal concentration in the case of most severe poisoning possibly exceeded this level.

#### II DISTRIBUTION OF MERCURY IN THREE PATIENTS WHO CAME TO AUTOPSY

Notwithstanding the frequency of poisoning from mercury bichloride, very few determinations of mercury in cases of this condition are on record. Lomholt,<sup>4</sup> in an exhaustive review, cited two series. The larger of these, that of Ludwig and Zillner, which included eight cases of mercuric poisoning, six of which were from mercury bichloride, dates from 1890, and an unsatisfactory method was used (*mit einer recht unvollkommenen analytischen Methode*—Lomholt). This leaves only Lomholt's own series of four cases, two being instances of acute poisoning with mercury bichloride and two, of chronic poisoning by inunctions. Somewhat more numerous studies have been made on animals,

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<sup>4</sup> Lomholt, Svend. Quecksilber, Theoretisches, Chemisches und Experimentelles, in Jadassohn, J. Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 18.

a good part also with unsatisfactory methods Lomholt pointed out that the values obtained in these various series agree sufficiently in their general features to permit general conclusions However, the quantities are not properly comparable, so that reliable data exist at present for only two clinical cases of poisoning with mercury bichloride A search of the "Quarterly Cumulative Index Medicus" and of *Chemical Abstracts* failed to locate any later analyses It seems most desirable to enlarge this number Through the cooperation of the departments of medicine and pathology at the hospitals of the university, opportunity was given to study three cases of the usual type, ending fatally in from six to nine days One of these cases (that of L R O) was included in the studies on excretion reported in the first part of this paper The analyses were restricted chiefly to the organs concerned with excretion and included the excreta, when obtainable, and the blood

The case reports are abstracted briefly, so far as they bear especially on the present study It may be premised that all the patients were treated with gastric lavage, generally with colonic irrigations and with injections of saline solution, according to indications Anuria and fatal uremia developed in all patients

#### REPORT OF CASES

CASE 1—L R O, a white man aged 49, took about 5.5 Gm of mercury bichloride He vomited within an hour (discordant accounts as to time and number of emeses) Gastric lavage was started in one and a quarter hours There was complete anuria from the sixth hour to the fifth day, then oliguria persisted until death occurred, on the ninth day This patient was also studied for elimination of mercury The total amount of mercury (in milligrams) recovered was in vomitus (specimens), 160.5, by gastric lavage, 28.5, in feces, passed in spontaneous stools and after enemas, 23.5, by colonic irrigations, 1.4, and in the urine, 9.7

CASE 2—J T N, a white man aged 41, took 2.5 Gm of mercury bichloride The patient vomited repeatedly within twenty minutes Gastric lavage was started within half an hour There was scanty bloody urine on the first day, then the patient became anuric There was bloody diarrhea Uremic coma took place on the sixth day, and death occurred

CASE 3—W M T, a white man aged 28, took 1 Gm (or more) of mercury bichloride He vomited within twenty minutes Gastric lavage was administered within half an hour Hematuria occurred within an hour Oliguria developed, with 350 cc of urine on the second day and 70 cc on the fourth day Death occurred on the eighth day

The histories of the three cases are closely similar They differ chiefly in the dosage of mercury bichloride (5.5, 2.5 and 1 Gm), and this may have been varied by the amount of vomiting All the patients died between the sixth and the ninth day It will be shown that the mercury content of the organs was strikingly similar for two patients, J T N and L R O For W M T it was about a third of

that of the other two. Considering both the duration of life and the mercury content, the ranking of the patients according to the severity of the poisoning would appear to be J T N > L R O > W M T. However, the results are sufficiently related to justify averages.

#### CONCENTRATION OF MERCURY

*Organs*—The concentration is shown comprehensively in table 6 for our three patients and for Lomholt's patients, individually and as averages, the median for the seven patients of both series (obtained by averaging the three or four central values) and the average for the eight patients of the Ludwig and Zillner series are given. The data for Lomholt's patients and ours agree so closely that averages are justified. The Ludwig and Zillner data show the same sequence, but they run distinctly higher than the others, presumably owing to the analytic method. They cannot, therefore, be averaged with the data for Lomholt's patients, but they appear consistent in themselves and support the general conclusions. The greatest divergence in concentrations is in the intestines, probably owing to unabsorbed mercury. The use of copious colonic irrigation seems to make our series the more reliable in this respect.

One of the most impressive features of the table is the surprisingly close quantitative agreement among the individual values for the seven patients of Lomholt's series and ours, notwithstanding the differences in the histories as to dose and length of time which elapsed before treatment. However, the dosage has a distinct effect, as reflected in the lower concentration of mercury found in case 3 (dose, 1 Gm) as compared with that found in cases 1 and 2 (doses, 5.5 and 2.5 Gm, respectively) and that in Lomholt's case 4, in which the patient died in six days, as compared with that in his case 2, in which the patient died in three days and therefore presumably absorbed a larger quantity. On the other hand, two of his patients (cases 1 and 3), who died after several months of treatment withunctions and who had an absolutely different history, showed concentrations intermediate between those for the two patients with acute poisoning observed by him in every organ except the intestines, in which the quantities appear high owing to the presence of unabsorbed mercury.

As for the individual organs, the kidneys invariably have the highest concentration. This holds also for the individual patients in the Ludwig and Zillner series and for all the animal series. The concentration in the liver ranks next. The other organs follow at a considerable distance. Taking the concentration in the kidneys as a measure of comparison for the combined figures on the seven patients observed by Lomholt and us and arranging the other solid organs in order of descending concentrations, the liver averages about one-half to two-thirds the con-

TABLE 6—*Concentration of Mercury in Human Beings with Mercury Poisoning* \*

	Investigators										Ludwig and Zillner,† Median of Eight	
	Sollmann and Schreiber				Lomholt					Average of the Four (L)		Combined,† Median of Seven
	Patient J T N Mercury bichloride	Patient L R O Mercury bichloride	Patient W M T Mercury bichloride	Average	Patient II Mercury bichloride	Patient IV Mercury bichloride	Patient I Mercury benzoate inunctions	Patient III Inunction				
Mercury compound												
Dosage of mercuric chloride, Gm	2.5	5.5	1	3								
Days before death	6	9	8	8	3	6	37	77				
Kidneys	3.50	3.32	2.38	3.07	7.0	1.60	6.31	3.39	1.54	3.79	8.12	
Liver	2.50	2.58	1.04	2.04	3.21	0.32	1.20	2.45	1.80	2.05	1.65	
Spleen					1.0	0.43	0.6	0.15	0.55	0.55	0.66	
Colon	0.51	0.283—	0.30	0.36	(1.98?)	0.86	0.46	0.20	0.51	0.49	1.85	
Ileum	0.41	0.21	0.20	0.27	0.85	0.37	0.64	0.21	0.51	0.43	15.19	
Duodenum	0.22	0.54	0.06	0.27						0.27		
Heart					0.30	0.24	0.37	0.30	0.30	0.30	0.12	
Skeletal muscle							0.25		0.25	0.25	0.07	
Lung					0.57	0.03	0.1	0.1	0.20	0.20	0.28	
Brain					0.17	0.10	0.15—		0.14	0.14	0.08	
Feces, last day	W W S + 2.72	0.23		1.48								
Bile		1.22	0.10	0.66						0.66	1.5	
Blood	0.10	0.12	0.015	0.08						0.08		
Peritoneal fluid		0.026		0.026								
Urine from the bladder		0.013		0.013								

\* The concentration in the organ is expressed in milligrams per hundred grams moist weight, that in the fluids, in milligrams per hundred cubic centimeters

† Fatal case described in paper I

‡ Lomholt, Schreiber and Sollmann



centration in the kidneys, the spleen, one-seventh, the intestines, one-ninth (there being no constant difference in the various levels), the heart, skeletal muscle and lung, about one-fifteenth, and finally the brain, about one twenty-seventh. In a single analysis made by Ludwig and Zillner bone ranks somewhat lower than spleen.

*Blood*—The concentration in the blood was 0.10, 0.12 and 0.015 mg per hundred cubic centimeters for our three patients (cases 1 to 3, respectively). The first two values represent about one thirtieth, and the last represents only about one one hundred and seventieth, of the concentration in the kidneys. The average in the blood of the three patients is 0.08 mg, about one fortieth of the concentration in the kidneys. The other series do not contain any analyses of the blood, but in fourteen patients undergoing energetic treatment withunctions Lomholt found a range of from 0.04 to 0.33 per hundred cubic centimeters, with a median of 0.11 mg. This is just about the same as for our fatal series showing that the concentration of mercury in the blood has fallen to an innocuous level before death. This would be expected from the general knowledge of the rapid rate with which extraneous dissolved substances leave the blood stream. The direct injury from mercury from which the patient dies on the ninth day is probably completed within one or two hours after the poison is swallowed, the further course consisting essentially of the secondary consequences of the early injury.

Comparison of the concentration in the blood and that in other fluids is instructive. It may first be noted that Lomholt found that in three patients the concentration of mercury in the blood serum and that in the corpuscles was practically the same, so the concentration in the whole blood may be taken also as that of the serum.

*Ascitic Fluid*—In the peritoneal fluid L. R. O. (case 1) showed a very low concentration of mercury, 0.026 mg per hundred cubic centimeters, a fourth or fifth of the level for blood. Lomholt found the concentration of mercury in the ascitic fluid of three patients treated withunctions to be from 0.02 to 0.06 mg, and therefore lower than that of the blood (from 0.04 to 0.33 mg).

*Urine*—For L. R. O. (case 1) the concentration in the bladder urine at autopsy was 0.013 mg per hundred cubic centimeters, only a tenth that of the blood. The daily output of urine was very small. In Lomholt's series of patients treated withunctions, the concentration of mercury in the urine (0.065 to 0.35 mg per hundred cubic centimeters) was generally higher than that in the blood for the same fourteen patients, but the difference in the medians was not great (urine, 0.163 mg, blood, 0.11 mg).

*Bile*—The concentration of mercury in the bile removed from the gallbladder at autopsy was 1.22 mg per hundred cubic centimeters in

the case of more severe poisoning (L O R) and 0.10 in the case of milder poisoning (W M T). This represents about one-half and one-tenth, respectively, the concentration in the liver and ten times and eight times the concentration in the blood. Lomholt did not analyze the bile. Ludwig and Zillner found 1.5 mg of mercury per hundred cubic centimeters in the bile of one patient, about one-fifth the concentration in the liver, and they found none in another patient with a lower concentration in the liver. The values and ratios in the two series are comparable. Both show a rather wide variation. In both, the patients with the higher concentration in the bile had the higher concentration in the liver, and two of our patients also had a higher concentration in the blood, the latter relation being the closer. However, the number is too small to establish these correlations, especially since it is not known how long the bile was retained in the gallbladder. In any case, how-

TABLE 7—*Amount of Mercury (Mg) Stored in the Liver and in the Kidneys*

Patients	J T N	L R O	W M T	Average
Dose of mercury bichloride, Gm	2.5	5.5	1	3
Days before death	6	9	8	8
Weight of liver, Gm	1,950	1,700	2,220	
Mercury, mg per hundred grams	2.5	2.58	1.04	
Mercury, mg in liver	48.8	43.9	23.4	38.7
Weight of kidneys, Gm	480	460	420	
Mercury, mg per hundred grams	3.5	3.32	2.38	
Mercury, mg in kidneys	16.8	15.2	10.1	14.0
Mercury, mg in the liver and kidneys	65.6	59.1	33.5	52.3

ever, the concentration of mercury in the bile is materially lower than that in the liver and materially higher than that in the blood.

Calculating the total daily biliary excretion by multiplying the concentration of mercury by the normal output of bile (from 500 to 1,100 cc) leads, in the one case (L R O) in which the figures are available, to higher quantities of mercury for the biliary excretion (from 6.1 to 13.4 mg) than for the excretion in the feces, which averaged 1.35 mg per day for the last five days of life. The contradiction might be explained by extensive reabsorption of mercury in the bile, but this is rather improbable in view of the fact that enteritis, diarrhea or scanty volume of bile may be present, as the patient is in a state of considerable shock, or that the bile from the gallbladder may become concentrated and therefore not represent normal bile. Consequently all that can be affirmed is that some mercury present in the feces comes from the bile.

*Liver and Kidneys*—The total mercury content of the liver and kidneys is shown for our patients in table 7. It is about three times as high in the liver as in both kidneys (the concentration being about one and a half to two times as high in the kidneys).

*Entire Body*—The total mercury content of the body after poisoning from mercury bichloride may be estimated with fair approximation from the data of table 1 by assuming an average mercury content of 0.30 mg per hundred grams, exclusive of the liver and kidneys, which gives an estimate of 180 mg of mercury for a person weighing 60 Kg. Adding the amount of mercury found in the liver and kidneys, about 60 mg, the total mercury content is approximately 240 mg. This amount closely approximates the acutely fatal parenteral dose for animals, from 4 to 10 mg per kilogram (equivalent to from 240 to 600 mg for a man weighing 60 Kg). As it is deposited in the organs the mercury is probably inactivated, but this quantity must have passed through the blood in active form fairly acutely, so that the coincidence is probably significant. However, if the same amount had accumulated gradually, as it does in mercurial therapy, its significance would be quite different.

#### CONCLUSIONS

The distribution of mercury was studied at autopsy in the organs of three patients who died of typical poisoning from mercury bichloride. The results confirm those given in the few reliable reports of cases in the literature. There is a surprising quantitative uniformity in the data for different patients, although the dosage has some effect. The concentration of mercury is uniformly highest in the kidneys (average, 3.8 mg per hundred grams of moist organ, using the medians of the reliable analyses given in the literature), the liver follows, with about one half to two thirds of the concentration in the kidneys, then the spleen, with one seventh, the intestines, with one ninth, the heart, skeletal muscle and lungs, with about one fifteenth (0.2 to 0.3 mg per hundred grams), and finally the brain, with one twenty seventh. The concentration of mercury in the blood was between 0.015 and 0.12 mg per hundred cubic centimeters, about one fortieth of that in the kidneys. The concentration in the ascitic fluid was even lower, that in the bile was variable but always higher than that in the blood and lower than that in the liver. The total mercury content of the liver was about three times that of both kidneys.

# CHOLESTEROL CONTENT OF WHOLE BLOOD IN PATIENTS WITH ARTERIAL HYPERTENSION

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The demonstration by Anitschkow <sup>1</sup> in 1912 that the feeding of pure cholesterol to rabbits produced lesions of the large arteries closely simulating human arteriosclerosis suggested the view, championed by the Aschoff school, that atheroma in man is primarily due to impregnation of the intima with lipid material. With the development of satisfactory methods for the measurement of the lipid content of the blood, many investigators have studied the cholesterol partition in the blood of persons with hypertension and arteriosclerosis, with the thought that the presence of a high cholesterol content might, in conformity with the experimental results, be of pathogenic significance in these conditions <sup>2</sup>. The demonstration of a consistent variance from the norm of the cholesterol metabolism in patients with hypertension, who are at least potentially subject to arteriosclerosis, might, besides helping to explain the close association which exists between these two conditions, disclose a new avenue for therapeutic approach.

The studies dealing with the cholesterol partition in the blood of patients with arterial hypertension have given conflicting results. As will be seen, many of them are open to serious criticism. In 1917 Denis,<sup>3</sup> using the method of Bloo<sup>1</sup>, found that the cholesterol content was not increased above normal in eighteen patients with hypertension, twelve of whom had arteriosclerosis. She also found that renal impairment unassociated with azotemia did not appreciably influence the cholesterol level. In the same year Gorham and Myers,<sup>4</sup> using their own

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1 Anitschkow, N, in Cowdry, Edmund V. Arteriosclerosis. A Survey of the Problem, New York, The Macmillan Company, 1933, p 271

2 The recent demonstration by Dr T H Paul of Boston (*Am Heart J* **10** 328 [Feb] 1935) that the escape of cholesterol into the lumen of a coronary artery from a ruptured atheroma may result in coronary occlusion by acting as an embolus increases our interest in the cholesterol problem.

3 Denis, W. Cholesterol in Human Blood Under Pathological Conditions, *J Biol Chem* **29** 93, 1917

4 Gorham, F D, and Myers, V C. Remarks on the Cholesterol Content of Human Blood, *Arch Int Med* **20** 599 (Oct) 1917

method and assuming the average normal cholesterol content of human blood to be 160 mg per hundred cubic centimeters of blood, studied twenty patients with hypertension, eight of whom had arteriosclerosis. The average cholesterol value for the group was 190 mg per hundred cubic centimeters, with high and low values of 270 and 150 mg, respectively.

In 1924 Pribram and Klein,<sup>5</sup> using the method of Authenreith and Funk, concluded, as the result of eighty-seven determinations, that most patients with hypertension have hypercholesteremia. No control determinations on normal persons were reported. Similar conclusions were reached by Westphal,<sup>6</sup> who found hypercholesteremia in 71 per cent of eighty cases, and by Richard and Roesch,<sup>7</sup> who made studies in a similar number of cases. These investigators used a modification of the method of Authenreith and Funk and the method of Grigaut, respectively. Apparently no control series were observed. The confusion introduced by the multiplicity of methods for the determination of the cholesterol content was emphasized by Weidman and Sunderman<sup>8</sup> who, in reviewing the normal values for cholesterol content in man and animals as given by approximately eleven methods in use up to that year, concluded that the various technics had been so habitually modified by succeeding workers as to give inconstant values for the normal content.

The occurrence of hypercholesteremia in patients with hypertension has likewise been reported by Weil, Guillaumin and Abricoff,<sup>9</sup> who in eighteen instances professed to find a relationship between the cholesterol level and the height of the blood pressure. However, they failed to give the method used, and their report contains no observations on controls. Alvarez and Neuschlosz<sup>10</sup> in 1931 studied the cholesterol content of the serum in patients with hypertension by a new technic. Such serum was brought in contact with a known amount of cholesterol for a period of twenty-four hours, and the change in cholesterol content was deter-

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5 Pribram, H., and Klein, O. Ueber den Cholesteringehalt des Blutserums bei arteriosklerotischem Hochdruck, *Med Klin* **20** 572 (April 27) 1924.

6 Westphal, K. Pathogenesis of Essential Arterial Hypertension. Cholesterol a Tonus-Increasing Substance in Essential Hypertension and Its Relation to Other Pathogenic Factors, *Ztschr f klin Med* **101** 584, 1925.

7 Richard, G., and Roesch, J. Amount of Cholesterol in Eighty Subjects with Hypertension, *Bull Acad de med, Paris* **95** 363 (March 30) 1926.

8 Weidman, F. D., and Sunderman, F. W. Hypercholesteremia. I. The Normal Blood Cholesterol Figures for Man and for the Lower Animals, *Arch Dermat & Syph* **12** 679 (Nov.) 1925.

9 Weil, M. P., Guillaumin, C. O., and Abricoff, L. Contribution a l'etude des obesés. L'état de plethore, *Ann de med* **23** 328, 1928.

10 Alvarez, C., and Neuschlosz, S. M. Untersuchungen über das Blutcholesterin bei arteriellem Hochdruck, *Klin Wchnschr* **10** 244 (Feb 7) 1931.

mined by means of tests made before and after this procedure. In twenty-one of the twenty-five cases in which tests were made there was less cholesterol in the serum after the twenty-four hour period than before, while in the serum of patients not suffering from hypertension the cholesterol level was found to be increased after twenty-four hours. This Alvarez and Neuschlosz interpreted as indicating a supersaturation (*Uebersättigung*) of serum by cholesterol in patients with arterial hypertension. Medvei,<sup>11</sup> in repeating these observations, found that the differences in saturation in his series did not significantly exceed the experimental error of the method. Furthermore, the average cholesterol level in untreated serum of fifteen patients with hypertension was  $154 \pm 9.56$  mg per hundred cubic centimeters as compared with an average level of  $119 \pm 4.57$  mg, the value obtained in a like number of observations on controls. This is the only study we have encountered in which statistical criteria were utilized, and the difference in values was not significant. Wacker and Fahrig<sup>12</sup> reported an increase of all lipid complexes of the blood in cases of arterial hypertension. Using the Authenreith and Funk technic, they found an average cholesterol value of 207.4 mg per hundred cubic centimeters in sixteen instances, as compared with an average value of 152.17 mg for nineteen normal persons. The statistical significance of this difference cannot be calculated from their data.

Recently Bruger and Poindexter<sup>13</sup> studied the cholesterol content of the plasma in patients with uncomplicated obesity. Rarely was an abnormal value, by their criteria, encountered in this group. Three of thirteen patients in whom the obese state was complicated by essential hypertension had hypercholesteremia, and in one obese patient with arteriosclerosis an increased plasma cholesterol content was observed. Bruger and Poindexter regarded these results as significant.

We believe that the contention of those who believe that hypercholesteremia accompanies arterial hypertension remains to be proved. The reported studies have been for the most part inadequately controlled. The normal range of values, including the experimental error of the method used, has not been determined by each investigator for himself, and the "error of sampling," as revealed by statistical analysis, has not received sufficient attention. Furthermore, in many of the studies, con-

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11 Medvei, C. V. Zur Frage des Blutcholesterins bei arteriellem Hochdruck, *Klin. Wchnschr.* **11** 414 (March 5) 1932.

12 Wacker, L., and Fahrig, C. Ueber die mineralischen und lipoiden Bestandteile des Blutserums bei der essentiellen Hypertension im Vergleich zu den physiologischen Verhältnissen, *Klin. Wchnschr.* **11** 762 (April 30) 1932.

13 Bruger, M., and Poindexter, C. A. Relation of Plasma Cholesterol to Obesity and to Some of the Complicating Degenerative Diseases (Diabetes Mellitus, Essential Hypertension, Osteo-Arthritis and Arteriosclerosis), *Arch. Int. Med.* **53** 423 (March) 1934.

ditions which of themselves are known to elevate the cholesterol content of the blood and which may accompany arterial hypertension have not been rigorously excluded. Among these conditions may be listed diabetes mellitus,<sup>14</sup> hyperthyroidism,<sup>15</sup> the nephrotic syndrome in glomerulonephritis<sup>16</sup> and obstructive disease of the biliary tract.<sup>17</sup>

In this study we have attempted to elucidate and obviate complicating factors and to present adequately controlled data with a statistical evaluation of their significance. It will be shown that in our series essential hypertension with or without arteriosclerosis was not accompanied by hypercholesteremia.

#### MATERIAL AND METHOD

Our series consisted of two groups of patients. Group 1 comprised fifty-three hospitalized patients in whom the systolic blood pressure consistently exceeded 150 mm of mercury. There were twenty-four men and twenty-nine women ranging in age from 22 to 90 years, the average age being 61.2 years. The patients received a uniform hospital diet. Evidence of arteriosclerosis was carefully sought for by palpation of peripheral arteries and fluoroscopic examination of the aorta. The state of the arterioles was judged by ophthalmoscopic examination of the ocular fundi. The degree and extent of vascular damage were arbitrarily graded on the basis of from 0 to 3 plus. The presence of inflammatory renal disease was rigorously excluded, and the status of renal function was determined by the following tests: (1) the dilution and concentration test of Volhard, (2) the phenol-sulphonphthalein test, (3) the test for urea clearance, (4) the creatinine test of Majors, and (5) the determination of the urea nitrogen content of the blood. Renal impairment was considered to be present if at least two of these tests gave abnormal results.

The basal metabolic rate was determined in forty instances. It is to be emphasized that this was done as a routine procedure. In no instance was there clinical evidence of thyroid dysfunction. The sugar content of the blood during fasting was determined in all but two of the patients. It was significantly elevated in only two instances, but the values for cholesterol were not abnormal, hence for the purposes of this study it was not deemed necessary to determine the dextrose tolerance.

Control determinations of the cholesterol content were made on a group of forty-five hospital and dispensary patients (group 2). This group consisted of twenty-five male and twenty female patients, varying in age from 17 to 81 years, with an average age of 49.8 years. Unfortunately it was impractical to study this group as carefully as the patients with hypertension, but so far as possible patients with minor ailments not due to a disturbance of metabolism were chosen. None of

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14 Gray, H. Lipoids in One Thousand Diabetic Bloods with Special Regard to Prognosis, *Am J M Sc* **168** 35 (July) 1924.

15 Hurxthal, L. M. Blood Cholesterol and Thyroid Disease. III. Myxedema and Hypercholesteremia, *Arch Int Med* **53** 762 (May) 1934.

16 Volhard, F., and Suter, F. *Nieren und ableitende Harnwege*, Berlin, Julius Springer, 1931, p. 314.

17 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*, Baltimore, Williams and Wilkins Company, 1931, p. 247.

the patients had hypertension, hypothyroidism, diabetes mellitus, nephritis or disease of the biliary tract

It should be noted that all the females in both groups had passed the menopause. Careful attention was paid to this point because Okey and Boyden<sup>18</sup> have demonstrated the profound changes occurring in the cholesterol level of the blood during the phases of the menstrual cycle.

In every instance, blood for the determination of the cholesterol content was drawn before breakfast. The method of Bloor, Pelkan and Allen<sup>19</sup> was used. The experimental error in our laboratory was found to be 5 per cent. Bloor<sup>20</sup> stated that the average normal content by this method is about 200 mg per hundred cubic centimeters of blood, with a range of between 100 and 230 mg.

## RESULTS

In table 1, the pertinent data are given for the patients with hypertension, and in table 2, those for the control group. The patients are listed in the tables according to increasing magnitude of cholesterol values.

The fifty-three patients with hypertension had an average cholesterol content of whole blood of  $167.5 \pm 3.0$  mg per hundred cubic centimeters. The values for the control group averaged  $177.3 \pm 4.6$  mg per hundred cubic centimeters. The difference in values, as indicating a trend, is not statistically significant. No patient in group 1 had a cholesterol level exceeding 230 mg per hundred cubic centimeters of blood, the upper limit of normal values according to Bloor. In the control group (group 2) one value of 230 mg and one of 282 mg per hundred cubic centimeters were encountered. Both of the patients suffered from malnutrition, a finding which is consistent with the conception that cachexia may cause hypercholesteremia.<sup>21</sup>

The spread of values for the two groups may be expressed graphically as curves of distribution (chart). The curve for the control group is "skewed," which probably indicates that more uncontrolled factors were at work in this group and that they tended to influence the cholesterol level primarily in one direction, i.e., to increase it. We may call attention to one of these factors, namely, divergence from average body weight.

Table 1 shows that of thirteen patients with hypertension with a cholesterol level exceeding 180 mg per hundred cubic centimeters of

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18 Okey, K., and Boyden, R. E. Studies of the Metabolism of Women. III. Variations in the Lipid Content of Blood in Relation to the Menstrual Cycle, *J. Biol. Chem.* **72**, 261, 1927.

19 Bloor, W. R., Pelkan, K. F., and Allen, D. M. Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, *J. Biol. Chem.* **52**, 191, 1922.

20 Bloor, W. R. Personal communication to the authors.

21 Peters and Van Slyke,<sup>17</sup> p. 245.

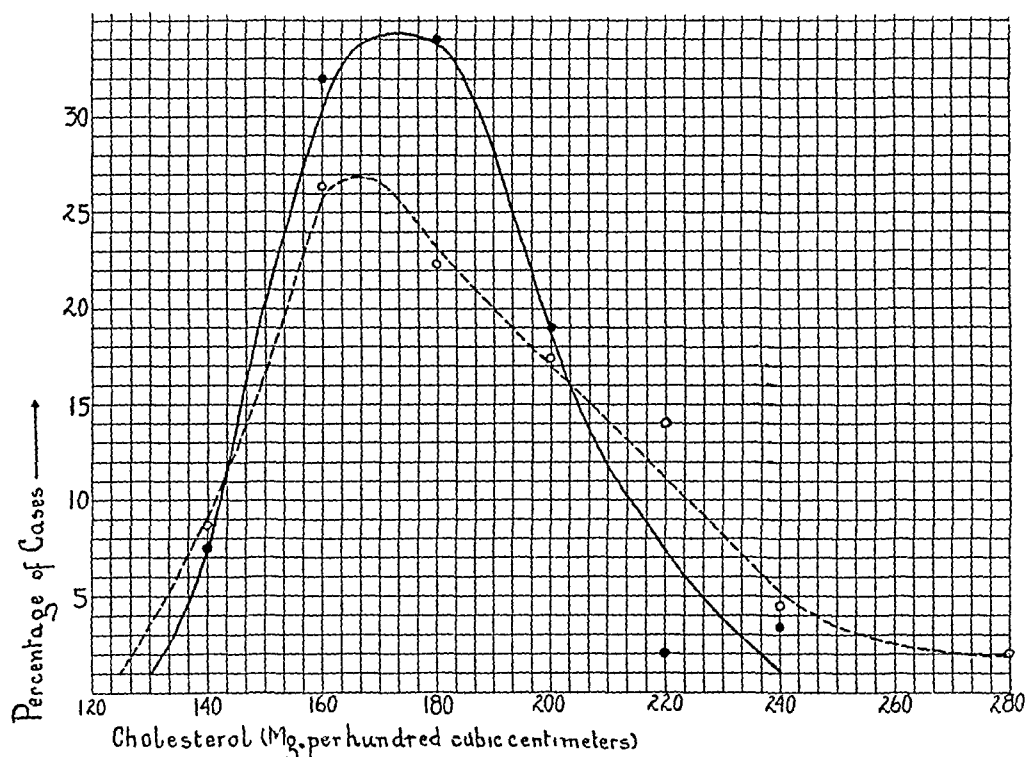


TABLE 1—*Values for Cholesterol and Pertinent Data on Fifty-Three Patients with Arterial Hypertension (Group 1)*

Pa- tient	Age	Sex	Average Blood Pressure	Known Dura- tion of Hyper- tension	Choles- terol, Mg *	Arterio- sclerosis	Renal Im- pair- ment	Percentage Over weight or Under weight	Basal Meta- bolic Rate	Sugar, Mg *	Urea Nitro- gen, Mg *	Calcium, Mg per 100 Cc of Serum
1	54	M	210/120	3 yr	125	+	+	+16	+ 0.9	124	14.8	10.3
2	40	M	160/ 80	?	129	+		0	-20.0	94		
3	54	M	200/110	1 yr	137	++		+ 8	?	110	13.0	11.1
4	63	M	165/105	?	139	++		+30	-19.0	120	11.1	11.2
5	46	F	200/100	4 yr	144	0		-12	- 2.0	92	15.0	9.6
6	80	M	210/130	10 yr	145	++	+	- 9	+20.0	104	38.4	9.6
7	75	F	215/115	?	145	+++		-20	?	120	16.0	?
8	72	F	180/100	?	145	++		+21	?	120	16.9	11.0
9	70	F	220/110	?	145	+		+18	+ 0.5	104	12.0	?
10	72	M	170/ 90	1 yr	145	++		+ 5	- 4.0	132	29.0	?
11	41	F	220/130	3 yr	145	+		+ 8	?	110	17.9	?
12	67	F	175/110	?	151	0		+33	-23.0	220	11.6	9.2
13	22	M	170/110	1 yr	152	0		+ 8	+ 2.0	112	17.1	?
14	67	M	150/100	8 yr	153	+		+ 4	-21.0	96	20.5	?
15	57	M	210/110	12 yr	154	+		- 5	- 8.3	110	14.3	9.0
16	63	F	170/110	10 yr	155	0		0	-23.0	94	11.0	11.4
17	51	M	220/160	10 yr	155	++		0	+ 5.0	124	12.7	10.2
18	62	M	170/110	?	155	+++		+ 5	- 2.2	110	23.0	?
19	52	F	160/ 85	?	155	0		+ 8	-30.0	92	13.0	?
20	63	M	220/110	5 yr	155	++		- 5	?	105	23.6	?
21	70	F	200/ 80	?	159	+		+20	- 7.7	104	15.4	12.5
22	49	F	255/150	8 yr	159	+		+38	- 0.9	128	13.3	11.1
23	57	M	200/100	6 yr	162	+		-	- 6.0	106	15.0	11.6
24	80	F	170/ 80	?	163	0		+ 4	?	138	10.7	10.1
25	73	M	220/130	4 yr	164	+++	+	- 4	- 4.0	108	15.3	9.7
26	79	F	230/ 90	10 yr	166	+		-16	?	110	16.9	?
27	60	F	180/ 80	?	166	++		-11	+15.6	126	13.4	?
28	62	M	205/105	4 yr	167	+	+	0	?	?	18.8	?
29	65	F	245/ 85	?	167	+		- 2	-12.0	120	15.0	?
30	68	F	210/115	15 yr	170	+		0	-13.0	104	18.8	?
31	69	M	165/ 95	?	170	0		-13	?	100	17.3	?
32	37	M	160/120	½ yr	171	++		- 5	-19.0	114	13.6	10.2
33	64	F	180/110	?	175	++		- 3	-10.0	104	21.4	?
34	59	F	180/110	10 yr	175	+		+17	-15.0	104	22.4	?
35	58	F	150/100	?	175	0		+64	-13.0	118	18.7	10.2
36	45	F	180/110	1 yr	175	0		+20	+ 1.0	120	15.3	?
37	65	F	155/ 85	?	180	0		0	-10.0	104	13.3	10.6
38	61	F	230/150	?	180	0		+43	-10.0	121	19.0	?
39	34	M	235/135	12	180	+	+	- 3	-24.0	110	31.0	?
40	90	M	215/ 90	?	180	+++		-15	?	108	20.7	?
41	60	F	175/100	?	182	+		- 3	- 2.0	110	13.1	10.4
42	56	M	170/110	8 yr	185	++		- 8	-10.8	104	15.0	10.0
43	66	F	170/ 90	6 yr	185	+		- 7	- 0.8	114	15.4	10.0
44	59	F	160/ 90	5 yr	185	0		- 2	+ 3.6	120	15.0	?
45	77	M	215/ 95	?	188	+		- 5	?	212	20.0	?
46	55	M	200/100	17 yr	191	+		-11	+10.0	102	17.6	10.2
47	74	F	155/ 90	?	195	+		+ 6	?	114	13.0	?
48	60	F	200/ 90	?	196	++		-18	+11.8	114	13.6	10.7
49	78	F	220/ 70	18 yr	196	++	+	0	?	136	13.6	9.8
50	58	M	220/110	7 yr	198	++		-13	+ 3.0	116	25.6	?
51	62	F	160/100	12 yr	203	+		-23	-12.0	104	15.6	9.7
52	50	F	180/110	?	222	0		- 6	- 5.0	?	16.6	?
53	73	M	155/ 90	?	222	++		-13	+ 5.0	106	13.3	?

\* The values for cholesterol, sugar and urea nitrogen are given in milligrams per hundred cubic centimeters of blood. The average value for cholesterol was  $167.5 \pm 3.0$ , that for calcium,  $10.3 \pm 0.17$ .

blood only one was slightly overweight, while the remainder were of normal weight or underweight. The average divergence from normal weight in this group was minus  $77 \pm 19$  pounds ( $349 \pm 086$  Kg), while in the remaining thirty-nine patients, it was plus  $68 \pm 28$  pounds ( $308 \pm 127$  Kg). This difference could occur by chance only once in several thousand times and hence cannot be without significance. However, all underweight persons in this group did not tend to have higher cholesterol levels (cases 5, 7, 26, 27 and others). We may interpret this as indicating that in a fair proportion of underweight persons some factor or factors, at present obscure, are at work which tend to elevate the cholesterol content of the blood.



Curves of distribution of cholesterol values for patients with and without hypertension. The solid dots indicate values for the patients with hypertension (group 1), and the open circles, those for the control group (group 2).

The same phenomenon was observed in the control group. It accounts in part at least for the "skew" in the curve of distribution previously mentioned, as an attempt was made to include in this group a large proportion of underweight persons. The average divergence from normal weight in nineteen patients in whom the cholesterol content of the blood exceeded 180 mg per hundred cubic centimeters was minus  $94 \pm 35$  pounds ( $426 \pm 159$  Kg), while the remaining twenty-six patients were heavier than the average normal weight by an average of  $13 \pm 34$  pounds ( $059 \pm 154$  Kg).

It is of interest that Gray<sup>14</sup> noted a similar phenomenon in diabetic patients. He found that the amount of blood fat, including cholesterol,

TABLE 2—*Values for Cholesterol and Pertinent Data on the Control Group*

Name	Age	Sex	Cholesterol, Mg per 100 Cc of Whole Blood	Percentage Over weight or Under weight	Diagnosis
J B	73	M	123	0	Coronary sclerosis
J E	21	M	133	-21	Asthma
B T	24	M	134	0	Normal
E N	49	F	138	-2	Normal
M B	38	M	142	+4	Fractured leg
J Y	17	M	144	-6	Normal
A D	39	M	146	+49	Peptic ulcer
B B	53	F	147	+11	Normal
R A	40	M	151	+16	Normal
C K	61	M	153	+4	Normal
L M	18	M	153	+9	Dementia praecox
J P	52	M	153	-11	Amnesia
A R	71	M	154	-12	Hypertrophy of the prostate gland
M H	59	F	156	-1	Normal
M D	62	F	156	+39	Cardiac failure
M K	49	M	160	+31	Normal
E G	44	F	164	-21	Normal
W C	50	M	168	-14	Normal
H K	56	F	168	-7	Mitral stenosis
E H	52	F	173	+16	Normal
M B	52	F	173	-2	Normal
I S	54	F	176	-18	Normal
F T	58	M	176	-6	Normal
J B	24	M	180	-1	Epilepsy
E P	42	M	180	-22	Pellagra (?)
B A	52	F	180	-11	Normal
H L	56	F	181	-40	Paranoia
G O	36	M	184	-21	Healed tuberculosis
C H	31	M	185	+10	Chronic bronchitis
E F	41	F	185	0	Neurasthenia
G E	81	M	188	+6	Herpes zoster
M D	34	M	190	-15	Peptic ulcer
E S	45	M	191	+16	Chronic iritis
H L	46	F	200	-27	Normal
C M	46	M	201	+4	Migraine
M O	76	F	202	0	Senile dementia
A D	72	F	202	-11	Senile dementia
A W	57	M	203	-24	Cardiospasm
H E	47	F	204	+4	Gastro enteritis
A E	40	F	206	-6	Angina pectoris
M F	75	F	218	-4	Senile dementia
W R	44	M	220	+3	Arthritis of the wrist
I T	60	F	226	-20	Fracture of the leg
F L	75	M	230	-35	Emaciation
J V	72	F	282	-20	Emaciation

The average value for cholesterol was  $177.3 \pm 4.6$

was 40 per cent higher in diabetic patients who were over 10 per cent underweight. He attributed this to more severe diabetes in these patients, but our data suggest that some factor other than diabetes alone must be taken into account.

In the last column of table 1 are listed the serum calcium values for twenty-five patients with arterial hypertension as determined by the Clark-Collip modification<sup>22</sup> of the Kramer-Tisdall method. These values bear no relation to the cholesterol level and all lie within the normal range of from 9 to 11 mg per hundred cubic centimeters. They are included in the table as a matter of interest, because some observers<sup>12</sup> have found a slightly lowered serum calcium level in patients with arterial hypertension.

*Influence of Arteriosclerosis on the Cholesterol Content of the Blood*—Thirteen of the 53 patients with hypertension had little or no evidence of vascular damage. The blood cholesterol level for the group averaged  $169.7 \pm 5.6$  mg per hundred cubic centimeters, with minimum and maximum values of 144 and 222 mg, respectively. For eighteen patients having from moderate to pronounced arterial disease the cholesterol content averaged  $164.0 \pm 4.8$  mg per hundred cubic centimeters, the lowest single value being 137 mg and the highest, 198 mg. In this group of patients, then, there was no correlation between the cholesterol content of the blood and the presence or absence of vascular disease.

*Correlation with Lowered Basal Metabolic Rate*—As previously noted, determination of the basal metabolic rate was conducted on forty of the patients with hypertension. In a surprisingly large number (42.5 per cent) the basal metabolic rate was lower than minus 10, reaching minus 20 or lower in six instances. None of these patients had the clinical symptoms of hypothyroidism or of any other endocrine dyscrasia. The average cholesterol content for the group with rates of minus 10 or lower was  $167.2 \pm 4.3$  mg per hundred cubic centimeters of blood, which is not significantly different from the average value of  $166.5 \pm 4.8$  mg for the remaining twenty-two patients with metabolic rates above minus 10.

These findings are of interest. We believe that the large number of low values for this group of patients is due in part at least to the fact that they were hospitalized during the determinations and that repeated readings were made until it was reasonably certain that a true basal metabolic rate was being measured. Hurxthal<sup>23</sup> recently emphasized the fact that a lowered basal metabolic rate is encountered in many conditions but that if true hypothyroidism is present it is quite uniformly accompanied by hypercholesterolemia. This finding is so constant that it may be used in differential diagnosis. Our results are in conformity

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22 Hawk, P. B., and Bergheim, O. *Practical Physiological Chemistry*, Philadelphia, P. Blakiston's Son & Co., 1931, p. 460.

23 Hurxthal, L. M. *Blood Cholesterol and Hypometabolism. Suprarenal and Pituitary Deficiency, Obesity and Miscellaneous Conditions*, Arch. Int. Med. **53**: 825 (June) 1934.

with this conception, at least so far as they clearly show that a lowered basal metabolic rate may be encountered in the absence of clinical hypothyroidism and that under these circumstances the blood cholesterol level is not elevated

#### CONCLUSIONS

The data presented in this study indicate that

Uncomplicated arterial hypertension is not accompanied by hypercholesteremia

Vascular degeneration and/or renal impairment occurring with arterial hypertension do not elevate the cholesterol level of the blood

Higher values for cholesterol are found more frequently among underweight than among obese persons

A low basal metabolic rate in persons with arterial hypertension, if unaccompanied by clinical symptoms of hypothyroidism, does not produce hypercholesteremia

Miss M. Louisa Long and Miss Elsie Hill gave technical assistance, and Dr. A. L. Koehler furnished data on some of his patients

# CHLOROPHYLL AND REGENERATION OF THE BLOOD

EFFECT OF ADMINISTRATION OF CHLOROPHYLL DERIVATIVES TO  
PATIENTS WITH CHRONIC HYPOCHROMIC ANEMIA

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Chronic hypochromic anemia is characterized primarily by a deficiency of hemoglobin. Iron is adequately effective in treatment, although this element composes only a small portion of the hemoglobin molecule. It is thus of interest to inquire whether other factors may be lacking besides iron and, if so, whether these factors when supplied can assist in the formation of hemoglobin.

In addition to a lack of iron there may occur sometimes a deficiency of other substances useful in the formation of hemoglobin, such as substances which occur in liver. Material contained in bile pigment perhaps may be wanting. Bile pigment<sup>1</sup> has been shown to exert a favorable effect on the regeneration of hemoglobin in cases of chronic hypochromic anemia. As a working hypothesis it has been assumed that the pigment aids in the synthesis of hemoglobin by supplying material suitable for the heme portion of the molecule. Because of the similarity of chlorophyll to this pigment, the present study has been made to determine the effect of chlorophyll and its derivatives on the regeneration of hemoglobin in cases of chronic hypochromic anemia.

## RELATIONSHIP OF CHLOROPHYLL AND HEMOGLOBIN

*Biologic Relationship* —For many years both the lay and the medical public have believed green vegetables to possess an indefinite but probable value in building blood. Abderhalden<sup>2</sup> in his textbook suggested that blood pigment might be made from plants. The fact that herbivora build hemoglobin on a diet composed of leafy greens invites the hypothesis that derivatives of chlorophyll may be used in making hemo-

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The expenses of this investigation were borne in part by a grant from the J. K. Lilly gift to the Harvard Medical School.

From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1 Patek, A. J., Jr., and Minot, G. R. *Am. J. M. Sc.* **188** 206, 1934.

2 Abderhalden, E. *Lehrbuch der physiologischen Chemie in dreissig Vorlesungen*, ed. 3. Berlin, Urban & Schwarzenberg, 1914.

globin. Certainly the ultimate products, that is to say amino-acids, must be used for this. Whether it is possible for the body to use building stones preformed from the food, such as the pyrroles or porphyrins, in the synthesis of hemoglobin has been neither proved nor disproved.

Much phyllo-erythrin, for example, appears in feces of cattle. Part, however, of this pigment derived from chlorophyll is recovered in bile,<sup>3</sup> which indicates some absorption. But, as Marchlewski<sup>4</sup> commented, there is no reason for assuming that chlorophyll can be used for the formation of hemoglobin. The absorption does not imply necessarily a useful purpose. Fischer and Hendschel,<sup>5</sup> indeed, expressed the opinion that it plays no part in nutrition. The cow has been shown to decompose chlorophyll in its third and fourth stomach to the porphyrin stage.<sup>6</sup> Its long intestine is well suited to the thorough digestion of the cellulose material that envelops the pigment. The cow, therefore, is able to utilize greenstuffs better than man. This may account for the failure to demonstrate in man a significant hemoglobin-enriching effect from feeding spinach and other greenstuffs. If benefit is derived from chlorophyll pigment in these foods it is probably by a slow process.

*Chemical Relationship*—Added to the biologic is a chemical relationship between chlorophyll and hemoglobin. This was suggested by Verdeil<sup>7</sup> in 1851 and substantiated in 1879 by Hoppe-Seyler,<sup>8</sup> who showed a similarity between hematin and chlorophyll derivatives. Later Nencki, Zaleski, Schunck and Marchlewski<sup>9</sup> obtained hemopyrroles from both sources. Until the time of Willstatter's work<sup>10</sup> (1906-1913), the exact nature of chlorophyll and its mineral component was not established. Willstatter recognized it as an unstable water-insoluble magnesium compound characterized by ester groups of methyl and phytyl alcohol. A knowledge of the molecular structure was gained through the research of Hans Fischer<sup>11</sup> and later elaboration by Conant<sup>12</sup>. The subject was reviewed recently by Schertz,<sup>13</sup> Armstrong<sup>14</sup> and Fischer<sup>15</sup>.

3 Broun, G. O., McMaster, P. D., and Rous, P. *J. Exper. Med.* **37** 699, 1923.

4 Marchlewski, L., and Urbanczyk, W. *Biochem. Ztschr.* **263** 166, 1933.

5 Fischer, H., and Hendschel, A. *Ztschr. f. physiol. Chem.* **198** 33, 1931, **206** 255, 1932, **216** 57, 1933.

6 Rothemund, P., and Inman, O. L. *J. Am. Chem. Soc.* **54** 4702, 1932.

7 Verdeil, M. F. *Compt. rend. Acad. d. sc.* **33** 689, 1851.

8 Hoppe-Seyler, F. *Ztschr. f. physiol. Chem.* **3** 339, 1879, **4** 193, 1880.

9 Marchlewski, L. *Die Chemie der Chlorophylle und ihre Beziehung zur Chemie des Blutfarbstoffs*, Braunschweig, F. Vieweg & Son, 1909.

10 Willstatter, R., and Stoll, A. *Untersuchungen ueber Chlorophyll*, Berlin, Julius Springer, 1913.

11 Fischer, H. *Ber. d. deutsch. chem. Gesellsch.* **60** 2611, 1927.

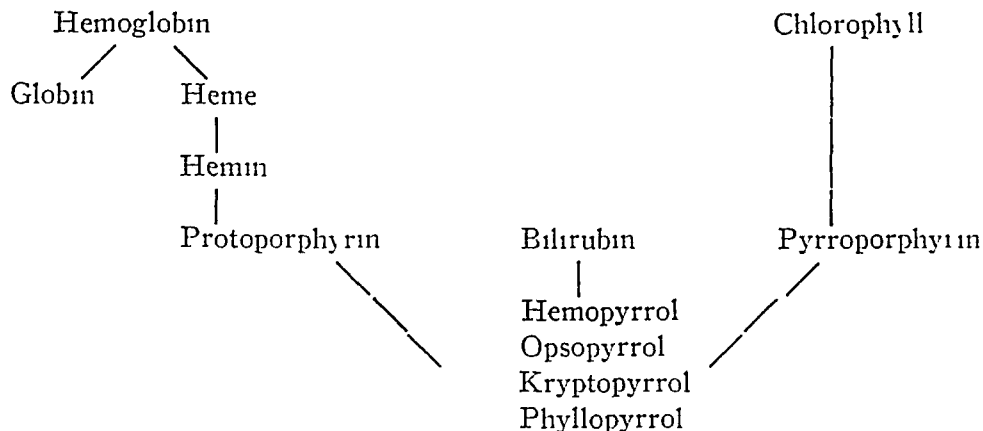
12 Conant, J. B., and Dietz, E. M. *J. Am. Chem. Soc.* **55** 839, 1933.

13 Schertz, F. M. *Quart. Rev. Biol.* **3** 459, 1928.

14 Armstrong, K. F. *Chem. & Indust.* **52** 809, 1933.

15 Fischer, H. *J. Chem. Soc. London* **1** 245, 1934.

The following diagram gives a scheme of the chemical relationship of hemoglobin, bilirubin and chlorophyll pigments



#### EXPERIMENTATION ON ANIMALS

The first person to attempt to demonstrate in animals a hemato-poietic effect of chlorophyll was Emil Burgi,<sup>16</sup> who in 1916 observed that rabbits rendered anemic by bleeding recovered more rapidly when chlorophyll was added to their diet. J. M. D. Scott<sup>17</sup> in 1923 noted that rats fed white bread, milk and leafy greens failed to have anemia after repeated small measured losses of blood, in contrast to rats that had been fed a diet of white bread and milk alone. E. Scott and Delor<sup>18</sup> in 1933 reported experiments in which the anemia of rats induced by a diet of milk was relieved by the administration of an iron-free and copper-free extract of alfalfa. Saunders<sup>19</sup> in 1926, Zih<sup>20</sup> in 1933 and others<sup>21</sup> reported on the regenerative effect on hemoglobin of feeding chlorophyll to animals with experimental anemia. On the contrary, Guerini<sup>22</sup> recently described a hemolytic effect resulting from photosensitivity after the intravenous injection of chlorophyll in albino rats.

The diverse results and interpretations of earlier writers are confusing. Most of the work was done before pure preparations of chlorophyll were available, and little effort has been made to exclude the possibility of side effects from mineral contaminants.

#### THE DISEASE IN MAN

A good diet has been considered requisite for the cure of nutritional hypochromic anemia. Yet the addition of iron alone to a minimal or

16 Burgi, E. *Cor-Bis schweiz Aerzte* **46** 449, 1916

17 Scott, J. M. D. *Biochem J* **17** 157, 1923

18 Scott, E., and Delor, C. J. *Ohio State M J* **29** 165, 1933

19 Saunders, C. W. *Proc Soc Exper Biol & Med* **23** 788, 1926

20 Zih, A. *Arch f d ges Physiol* **231** 510, 1933

21 Aoki, S. *Sei-I-Kwai M J* **50** 1, 1931, abstr., *Chem Abstr* **26** 3847  
 1932 Sagastume, C., and Pezzani, J. *Rev Facult d cienc quim, Univ la Plata* **7** (pt 2) 7, 1930, abstr., *Chem Abstr* **25** 3080 1931

22 Guerrini, G. *Boll d Soc ital di biol sper* **7** 835, 1932



even to an inadequate diet corrects the anemia rapidly. How does it do this when globin and heme pigments are involved in the synthesis of hemoglobin? If a patient with anemia is given a diet rich in meat, greens and fruit one does not see a sharp response in the hemoglobin content or the red blood cell count. The hemoglobin content, however, that one estimates from a sample of the peripheral blood does not necessarily reflect the underlying state of the tissue, such as the blood reserve. There is obviously a blood potential in the total organism which a determination on a sample of blood may not indicate. A "good" diet, then, might be useful in a way which the present standards of measure do not show, at least in a short space of time.

The problem is not so much whether factors other than iron do play a rôle as whether they can play a rôle in the formation of hemoglobin. If it can be shown that certain substances beside iron influence the regeneration of hemoglobin in hypochromic anemia in man, as Whipple demonstrated that they do in dogs, and that these substances exert their influence in some manner other than furthering the absorption of iron it is permissible to suppose that such substances may take part in the regeneration of hemoglobin. Otherwise it is implied that the body makes no use of these preformed substances but rather synthesizes them.

Except for reports by Burgi<sup>23</sup> and his co-workers,<sup>24</sup> little has been recorded in the literature concerning the clinical trial of chlorophyll in the treatment of anemia. Burgi and his associates recommended it not only in cases of anemia but also in cases of tuberculosis, cardiac disease, arteriosclerosis and mental depression because of its "tonic" benefit. Burgi's preparation chlorosan and other proprietary remedies purporting to contain chlorophyll have been found on analysis to contain a trivial amount of the substance. For these reasons one regards Burgi's clinical reports with skepticism.

#### PROGRAM AND METHODS

The present study concerned fifteen adult patients with chronic hypochromic anemia who were given chlorophyll and allied substances. Chronic hypochromic anemia serves well in the study of the regeneration of hemoglobin because the hemoglobin content is reduced much more than the red blood cells. It is a chronic disease and little subject to spontaneous fluctuation in the state of the blood. Consequently, any changes occurring during therapy in such patients would seem to be part of a causative sequel. The patients were given a house diet free from meat and eggs. Whereas it was adequate in other respects, the diet was shown in previous studies not to cause improvement of the condition of the blood in such cases. The red blood cell count, the concentration of hemoglobin and the percentage of reticulocytes were determined frequently for a control period of a week before therapy was begun. The initial red cell counts varied from 2,200,000 to 4,600,000 per cubic millimeter, and the hemoglobin content varied from 22 to

23 Burgi, E. *Das Chlorophyll als Pharmakon*, Leipzig, Georg Thieme, 1932.

24 Zickgraf, G. *München med Wchnschr* 79 998, 1932.

58 per cent (Sahli) These determinations were made on alternate days on venous blood Reticulocytes were counted daily on from 1,000 to 2,000 red blood cells

Since the reaction of the reticulocytes is a sensitive index of the potency of the material administered to patients with anemia, the course taken by these young red cells was followed closely This measure allows one to learn promptly the response to therapy, whereas the concentrations of the hemoglobin and the red cell count may lag considerably In this way one may test the potency of different substances in succession on the same patient, which is a more valid procedure than to compare the response in one patient to that in another By using the same patient for testing different materials, one period of observation serves as a control for the ensuing period

Heretofore it has been shown that if a suboptimal dose of iron is followed by a larger dose a second reticulocyte response will occur The validity of this comparative test was discussed by Heath<sup>25</sup> and Minot<sup>26</sup> With this in mind, preparations of chlorophyll were given with iron after a period of medication with the latter alone, in order to see what further response, if any, they might effect

#### PREPARATIONS USED<sup>27</sup>

There are two difficulties concerning the clinical use of preparations of chlorophyll The first is to obtain a pure preparation, because leafy greens contain minerals, salts, vitamins and other substances in addition to chlorophyll The chlorophyll content varies markedly with the season, the type and the condition of the plants It would be impossible, therefore, to conclude from the feeding of greenstuffs what role is played by chlorophyll The second difficulty is that pure chlorophyll is unstable and insoluble in most solvents With it one can create only a finely dispersed state Whatever is absorbed by feeding must be a small portion of the material administered Just as insoluble preparations of iron are relatively ineffectual in the treatment of hypochromic anemia because of difficulty in absorption, the feeding of an insoluble material like pure chlorophyll could not be expected to produce significant changes in the blood Reports of negative effects from the use of pure chlorophyll or pheophytin would not be surprising Sodium chlorophyllin, a soluble salt, was therefore used by preference in this study A further degradation product, chlorin *c*, which is likewise soluble, was tried parenterally

The crude chlorophyll used was a tarlike paste extracted from alfalfa leaves Natural contaminants were present, such as xanthophyll, fucoxanthin and carotinoid pigments In five instances the material was fed in capsules In a sixth instance it was given in 50 cc of water to which 3 cc of a 10 per cent solution of sodium hydroxide had been added for each 10 Gm of paste This made a homogeneous mixture, but it was unpalatable

Pheophytin is pure chlorophyll from which the magnesium radical has been split off Since pure chlorophyll loses this magnesium radical in the stomach by interaction with hydrochloric acid, pheophytin virtually had the same significance

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25 Heath, C W Oral Administration of Iron in Hypochromic Anemia, Arch Int Med **51** 459 (March) 1933

26 Minot, G R Tr A Am Physicians **49** 287, 1934

27 The American Chlorophyll Company supplied pheophytin and sodium chlorophyllin The crude chlorophyllin was supplied by Smith, Kline and French Dr Emma Dietz, of the Converse Laboratory, Harvard College, prepared the chlorin *c*

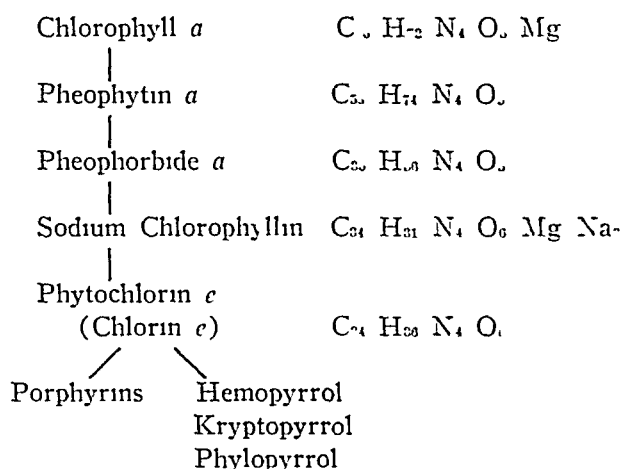
in these studies as pure chlorophyll. In three instances it was fed in capsules. In a fourth it was given in oil, but this was unpalatable.

Sodium chlorophyllin is a water-soluble salt containing the magnesium radical. It was given in solution and was not found distasteful.

Chlorin *c* is a water-soluble degradation product which lacks the magnesium radical. This was neutralized by the addition of a few drops of concentrated sodium hydroxide until  $pH$  7.4 was reached. It was then passed through a Berkefeld filter and stoppered in air-tight sterile bottles. Each cubic centimeter contained 0.02 Gm. of the solid material. Intragluteal injection caused moderate local pain and discoloration of the buttocks. The addition of procaine hydrochloride to the solution of chlorin *c* afforded relief.

An analysis of the iron content of these preparations was as follows: in crude chlorophyll, 23 mg. of iron per hundred grams; in pheophytin, 200 mg. of iron per hundred grams; in sodium chlorophyllin, 40 mg. of iron per hundred grams; and in chlorin *c*, 165 mg. of iron per hundred grams. Therefore the amount of iron contained in the largest daily dose of these products was: for crude chlorophyll (4 Gm.), 0.9 mg. of iron; for pheophytin (15 Gm.), 3 mg. of iron; for sodium chlorophyllin (15 Gm.), 0.6 mg. of iron; and for chlorin *c* (0.1 Gm.), 0.016 mg. of iron. These amounts were relatively insignificant, since the smallest dose of ferric ammonium citrate prescribed (0.6 Gm.) contained 102 mg. of iron.

The composition of the five substances listed showed the following relationships:



#### OBSERVATIONS

*A Chlorophyll Products Alone*—In two separate series of observations on the same patient pheophytin was fed in amounts averaging 1 Gm. daily for seven days, without effect on the red blood cell count, the concentration of hemoglobin or the reticulocyte count. Negative results were noted also in two patients fed sodium chlorophyllin daily in amounts averaging 15 Gm. daily for seven days. In one case 5 cc. of chlorin *c* was injected intramuscularly daily for five days without effect.

*B Disproportionate Amounts of Chlorophyll and Iron (Administered Orally)*—In three series of observations on two patients a trial period of treatment with ferric ammonium citrate in daily doses of 0.6, 0.6 and 1.8 Gm., respectively, was given for ten days. In the first case a moderate response of reticulocytes occurred; in the two others only a slight response took place. With this medication continued crude chlorophyll was added in amounts of 3, 4 and 4 Gm., respectively, for ten days, but an additional effect was not observed. Thus very small doses of iron with relatively large doses of chlorophyll were no more effective than iron alone.

TABLE 1—Results in Six Cases of Chronic Hypochromic Anemia of Administering Iron and Chlorophyll Products After a Period of Therapy with Iron Alone

Days of Treatment	0.6 Gm Daily* Case 1			4 Gm Daily† Case 2			1.5 Gm Daily Case 3			0.6 Gm Daily Case 4			1 Gm Daily Case 5			1 Gm Daily Case 6†		
	Period 1			Period 1			Period 1			Period 1			Period 1			Period 1		
	Red Blood Cells, Million Cent	Hemo globin, per Cent	Reticu loytes, per Cent	Red Blood Cells, Million Cent	Hemo globin, per Cent	Reticu loytes, per Cent	Red Blood Cells, Million Cent	Hemo globin, per Cent	Reticu loytes, per Cent	Red Blood Cells, Million Cent	Hemo globin, per Cent	Reticu loytes, per Cent	Red Blood Cells, Million Cent	Hemo globin, per Cent	Reticu loytes, per Cent	Red Blood Cells, Million Cent	Hemo globin, per Cent	Reticu loytes, per Cent
0	4.63	50	1.2	5.0	59	1.4	2.30	37	1.0	2.68	25	1.1	3.36	42	0.9	2.70	29	2.2
2		51	1.7		60	2.0		39	2.3			2.1		41	0.5		28	1.6
4		51	1.2		61	2.8		40	4.7		2.3	1.0		43	0.8		32	2.9
6		51	1.6		61	6.8		42	10.1			2.0			2.0		35	3.5
8		52	1.6		62	10.3		42	11.5			1.6		42	1.0		35	3.5
10		53	1.3		65	2.2		43	8.0		2.70	1.8		44	0.9		39	4.7
12								45	4.8									2.5
14							3.67	47	2.8							3.31	40	1.7
Period 2																		
Oral Administration of Chlorophyll Products in Addition to the Same Amounts of Iron and Ammonium Citrate as in Period 1																		
Sodium Chlorophyllin, 0.6 Gm Daily 5 Days																		
2	5.01	57	1.9	5.16	71	2.3	3.67	48	1.0	2.70	24	1.9	3.55	45	3.4	3.50	45	2.1
4		59	3.3		73	6.6		50	9.9		24	5.8		48	3.0		45	3.6
6		60	1.7		71	7.3		54	4.3		29	6.0		48	2.1		49	4.3
8		62	2.1		74	4.9	3.88	55	3.0			4.8		50	1.3		50	1.8
10			0.8		75	4.4			1.5	3.50	30	1.1			1.0	3.80	49	0.7
12	5.02	59	1.4			4.0								51	1.2			
14					74	3.6												
16				4.90	76	2.2												

\* For the sake of brevity only the bidaily data are recorded. The periods are consecutive

† In case 2 the studies were made on the same patient as in case 1, but when the concentration of hemoglobin was at a higher level

‡ In case 6 a ten day period with 1 Gm daily of crude chlorophyll, followed directly after the second period with pheophytin. A similar and further rise of the hemoglobin content (7 per cent) and a reticulocyte response took place

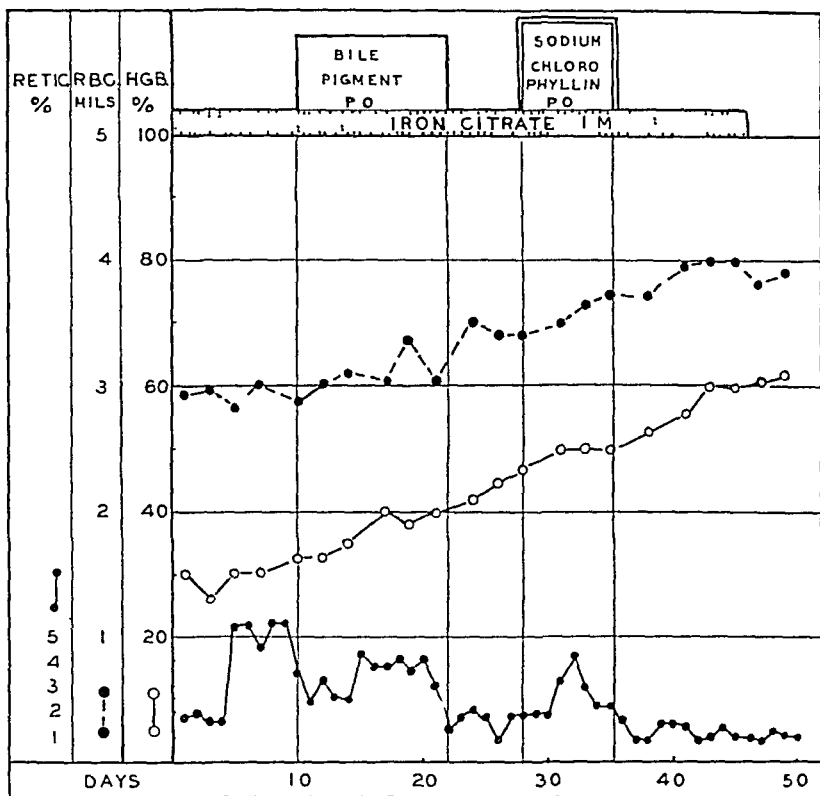


Chart 1—Changes in the blood in a case of chronic hypochromic anemia following the administration of iron, bile pigment and sodium chlorophyllin. Note that bile pigment, a related pigment substance behaves similarly to the chlorophyll derivatives.

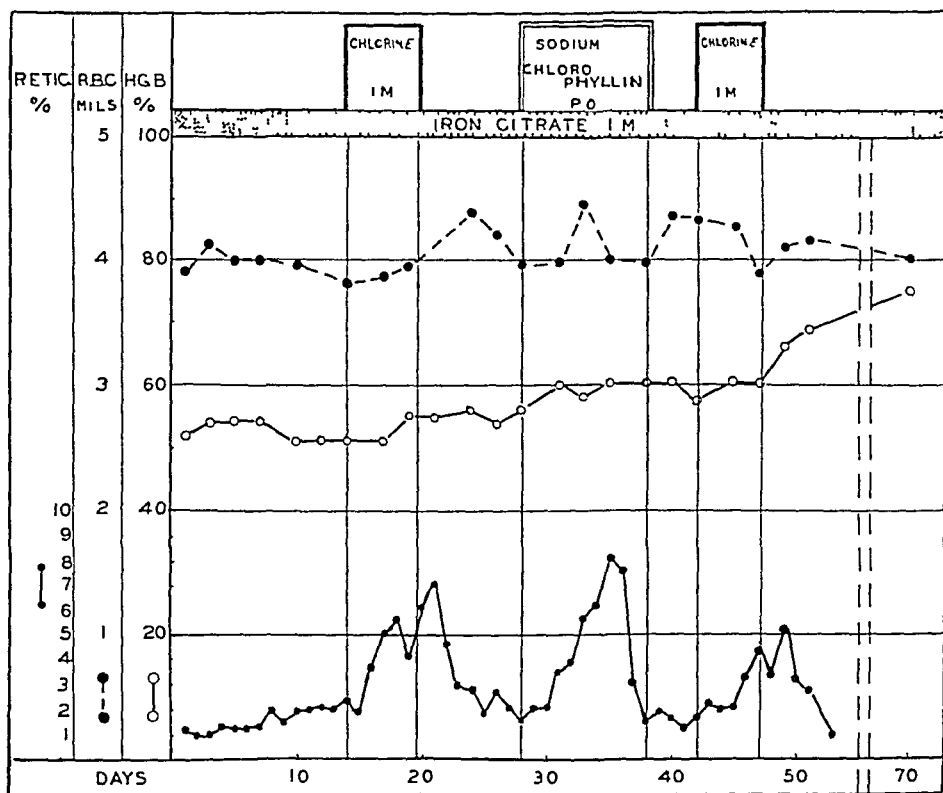


Chart 2—Changes in the blood in a case of chronic hypochromic anemia following the administration of chlorophyll derivatives and iron. Iron citrate and chlorin *c* were given intramuscularly and sodium chlorophyllin orally.

*C Comparable Amounts of Chlorophyll and Iron (Administered Orally) —*

In seven series of studies on five patients ferric ammonium citrate in suboptimal doses was given daily for at least ten days, during which the usual response of reticulocytes occurred, with the peak between the fifth and the eighth days. Iron medication was continued, and a chlorophyll product was added in daily amounts comparable by weight to the dose of ferric ammonium citrate. In all instances a second reticulocyte response occurred, with the peak on about the fifth day. There were three trials with crude chlorophyll, two with pheophytin and two with sodium chlorophyllin. During the first period of about ten days with iron alone, the average percentage gain in concentration of hemoglobin was 4.6 per cent, and during the second period, 7.8 per cent. These figures allow only a rough estimate of the gain in concentration. In short intervals there may be a lag of response, so that one period overlaps the succeeding period. However, it appears that the rate of increase of concentration of hemoglobin with iron and chlorophyll therapy

TABLE 2—*Analysis of the Results of Administering to Patients with Chronic Hypochromic Anemia Iron and Chlorophyll Products, Both Separately and Combined and Orally and Parenterally*

Test Materials*		Results	Number of Observations
A	Pheophytin alone	Negative	2
	Sodium chlorophyllin alone	Negative	2
	Chlorin <i>e</i> alone (1 m)	Negative	1
B	Iron and crude chlorophyll in disproportionate amounts†	Negative	3
C ‡	Iron and crude chlorophyll	Positive	3
	Iron and pheophytin	Positive	2
	Iron and sodium chlorophyllin	Positive	2
D	Iron (1 m) and sodium chlorophyllin	Positive	2
E	Iron (1 m) and chlorin <i>e</i> (1 m)	Positive	3

\* Substances were given orally unless otherwise indicated, 1 m means intramuscularly. A positive result signifies an observation in which after a test period with iron the addition of a chlorophyll product was followed by a second response of reticulocytes.

† This refers to cases in which small amounts of iron and relatively large amounts of chlorophyll were given, as mentioned in the text under observations B.

‡ The results in group C are recorded in detail in table 1, those in groups D and E are given in charts 1 and 2.

exceeds that with iron alone. The data for these observations are recorded in detail in table 1.

*D Iron Given Intramuscularly with Sodium Chlorophyllin by Mouth*—In a series of studies on two patients 0.1 Gm. of iron citrate was injected intramuscularly daily for ten days. Moderate response of the reticulocytes occurred. With the identical therapy continued, sodium chlorophyllin was fed by mouth, to one patient 0.7 Gm. was administered daily for eight days, and to the other, 1 Gm. daily for six days. A second reticulocyte response took place promptly, which indicated that the combined effect was more potent than that of iron alone. These clinical observations are illustrated in charts 1 and 2.

*E Iron and Chlorin e Given Intramuscularly*—In a series of three studies on two patients iron citrate in doses of 0.1 Gm. daily was injected intramuscularly for ten days. A small reticulocyte response occurred. With this therapy continued, chlorin *e* was injected daily in doses of 5 cc. for five days. Each injection corresponded to 0.1 Gm. of the solid material. A second, sharp rise in the reticulocyte count occurred in both instances. The observations on one patient are illustrated in chart 2.

Data for the results in all the tests made with chlorophyll products are given in table 2, which is included for the sake of clarity.

## COMMENT

Several possible causes may be considered to explain the ineffectiveness of chlorophyll derivatives alone. In certain cases of anemia there may exist a state of pure deficiency of iron, there may be no want of pyrrol or of pigment substances, and in such instances one would expect no benefit from chlorophyll therapy. Since the materials in crude chlorophyll and pheophytin are relatively insoluble, there would arise also the question of embarrassment of absorption from the gastro-intestinal tract. However, the soluble chlorophyllin salt administered orally and chlorin *e* administered parenterally likewise failed to affect the blood picture when given without iron. It is apparently essential, therefore, that iron be present before a chlorophyll substance can be utilized. Iron salts are involved in the formation of chlorophyll, although they do not enter into its molecular structure. Emerson<sup>28</sup> and Noack<sup>29</sup> showed that the growth of chlorophyll in plants can be controlled by the presence of iron salts. An analogous catalytic effect perhaps takes part in the formation of hemoglobin.

It is known that chlorophyll combines chemically with iron in the ratio of about 10 molecules to 1. In those cases in which there was a response to therapy this ratio was never exceeded, the highest being 9 to 1. In the cases in which there was no response, with a large excess of chlorophyll, the ratio to iron was as high as 35 to 1. It may be that in the latter cases iron was fixed or buried because of the strong affinity for chlorophyll and thus became unavailable for absorption from the gastro-intestinal tract.

In those cases in which a second reticulocyte response occurred together with an increased rate of regeneration of hemoglobin following the administration of chlorophyll derivatives and iron, the response appears to have been significant. A reticulocyte response occurs, to be sure, as the result of hemolysis, but signs of this were not observed. The significant second responses occurred on the addition to iron medication of chlorophyll, sodium chlorophyllin, pheophytin and chlorin *e*. In the latter two substances the magnesium radical is missing. In all preparations iron was present in insignificant traces. Hence it is illogical to consider that a mineral contamination of iron or magnesium is responsible for the increased hematopoiesis observed. The fact that similar phenomena occurred when material was administered parenterally excludes a change of gastro-intestinal absorption as the conditioning factor when material was given orally.

Nonspecific agents like potassium arsenite can provoke reticulocytosis. Unexplained spontaneous fluctuations in the reticulocyte count

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28 Emerson, R. Proc Nat Acad Sc **15** 281, 1929

29 Noack, K. Naturwissenschaften **17** 104, 1929

also occur rarely. In the patients given chlorophyll and its derivatives, however, there was a rhythmic pattern of hematologic response. The time of onset of the response and the course taken by the reticulocyte count, the increase of concentration of hemoglobin and the improved sense of well-being were similar in all the patients in whom a response occurred. For these reasons it seems likely that the changes observed were not accidental and that the substances used provided a specific hematopoietic stimulus. Whether they acted in the intermediary stage of iron metabolism, that is, utilization of iron, or whether they acted simply in a substitutive way was not ascertained.

The study at least suggests that the human body can use preformed pyrrol substances in the building of hemoglobin. It is important to emphasize that such substances are not recommended for a therapeutic purpose. Iron therapy alone is adequate treatment in most cases of uncomplicated chronic hypochromic anemia. This study may serve to encourage the use of a diet ample in greenstuffs and protein foods, for it must be that over a long space of time favorably nutritious elements are absorbed which aid the blood reserve and which furnish building stones for the heme pigments necessary to the formation of hemoglobin.<sup>30</sup>

#### SUMMARY AND CONCLUSIONS

Twenty series of observations on fifteen cases of chronic hypochromic anemia were made with the aim of determining what effect the administration of chlorophyll products might produce on regeneration of the blood.

In five instances the administration of chlorophyll and its degradation products alone did not produce changes in the blood.

In three instances the administration of very large doses of crude chlorophyll with very small doses of iron likewise did not produce change in the blood.

In twelve sets of observations on nine cases the administration of chlorophyll products after a period of medication with comparable

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<sup>30</sup> In one patient fed 1 Gm of sodium chlorophyllin daily for eight days a marked cutaneous photosensitivity on the dorsum of the hands, on the tip of the nose and on the lips developed on the seventh day, although hematoporphyrin was not demonstrated. By avoiding exposure to sunlight for sixty days the lesions cleared. There were no systemic untoward effects.

Among other biologic functions, chlorophyll serves as an absorber of light energy to be used in photosynthesis. It is not unlikely that this patient's sensitivity was related to the medication. It so, it constitutes a danger in the use of chlorophyll for therapeutic purposes. A fuller exposition of this case is being prepared for a separate communication.



amounts of iron was followed by an orderly and significant increase in the concentration of hemoglobin and a second reticulocyte response

This combined effect was produced when materials were given parenterally as well as orally

The studies suggested that the body can use preformed pyridol substances for the building of hemoglobin

# CYTOLOGIC EXAMINATION OF NASAL SMEARS OF SENSITIZED AND NONSENSITIZED PERSONS WITH NASAL SYMPTOMS

WITH SPECIAL REFERENCE TO THE EOSINOPHIL COUNT AND  
TO SIMULTANEOUS BLOOD COUNTS

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The local accumulation of eosinophil cells in the tissues and sputum of persons afflicted with bronchial asthma was one of the observations of long ago. At first only the fact of its occurrence was known, now it seems to be well established that it is one of the phenomena of the sensitized or allergic state. The occurrence of increased numbers of eosinophil cells in the sputum of persons with tuberculosis,<sup>1</sup> bronchitis,<sup>2</sup> or bronchiectasis,<sup>3</sup> in gonorrheal discharge,<sup>4</sup> in the muscle of persons with trichinosis, in blisters produced by cantharides,<sup>5</sup> in the tissues of the intestinal tract and in the blood of persons with certain parasitic infestations, in carcinomatous tissue<sup>6</sup> and in the tissue of the pituitary gland in persons with certain disturbances of that gland is too well known to justify detailed comment. Various interpretations of this increase in the number of eosinophil cells have been given. However, since the early work on serum disease and anaphylaxis, it has become generally accepted that eosinophilia in the blood and in the tissues is characteristic during the manifestations of sensitization. Some observers have even gone so far as to express the opinion that all eosinophilia of the tissues, with the exception of the normal eosinophilia of the thymus, is the result of an allergic condition.

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A preliminary report was made at the meeting of the University of Michigan Pediatric and Infectious Disease Society, Nov. 18, 1933.<sup>12</sup>

From the Sensitization Division of the Department of Pediatrics and Infectious Diseases, and the Student Health Service, the University of Michigan.

1 Teichmüller, W. *Centralbl f inn Med* **19** 305 (April 2) 1898.

2 Grouven, C. *Ueber die eosinophilen Leukocyten der Schleimhaut des Respirationstractus*, Inaug. Dissert., Bonn, C. Georgi, 1895.

3 Fuchs, E. *Deutsches Arch f klin Med* **63** 427 (Aug. 18) 1899.

4 Vorbach, F. *Eosinophile Zellen bei Gonorrhoe*, Inaug. Dissert., Würzburg, 1895.

5 Bettman. *München med Wchnschr* **45** 1229 (Sept. 27) 1898.

6 Przewoski, E. *Centralbl f allg Path u path Anat* **7** 177 (March 15) 1896.

Our interest was awakened by the work of Huber and Koessler<sup>7</sup> (1922) on the pathology of asthma and that of Eyermann<sup>8</sup> and of Johnson and Goldstein<sup>9</sup> on the cytologic examination of nasal secretions of persons with hay fever and acute infections of the respiratory tract. Three years ago we began to record the differential cell counts of the nasal discharge of patients coming to the clinics for treatment of sensitization of the University Hospital and Student Health Service. We made no attempt to follow the differential counts from day to day. We were particularly interested to note in the several groups examined as a routine the frequency of the presence of eosinophil cells and the comparative number. All cell types were looked for, but the method of preparation and of securing material for examination may have been inadequate for the study of certain cell forms sometimes encountered that might show up better by the vital staining method. Wright's stain was used in all instances. Because of the large amount of mucus present it was necessary to stain the material longer than is usual for blood films.

Smears were made directly from the nostrils by means of a swab, a glass rod with a rounded end or a platinum loop or, as in most instances, by having the patient blow his nose on glazed paper or oiled silk. The material was spread thinly on glass slides or on cover slips and was stained in the same way as are blood films. From 100 to 200 cells were counted with the oil immersion lens. The cells had a tendency to gather in clumps and were often seen to stand out as reddened areas. One might search for some time, finding only here and there an eosinophil or a polymorphonuclear cell and then suddenly encounter a clump of 10 or more. With the mechanical stage one soon learns to run over the slide with considerable rapidity. In cover slip smears it may be necessary to examine more than one preparation to secure the total number, but this is unusual after one learns how the spreading should be done. It is of interest to note that in the sections of tissue studied by Huber and Koessler the eosinophil cells were usually found in nests along with other cells. Care must be taken not to mistake free nuclei of squamous epithelial cells for mononucleated leukocytes. These cells are often granular and sometimes take the eosin stain, but of course their morphologic characteristics at once differentiate them. In our counts we ignored cells other than those that belonged in the leukocyte group.

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<sup>7</sup> Huber, H. L., and Koessler, K. K. The Pathology of Bronchial Asthma, *Arch Int Med* **30** 689 (Dec) 1922.

<sup>8</sup> Eyermann, C. H. *Ann Otol, Rhin & Laryng* **36** 808, 1927.

<sup>9</sup> Johnson, M. C., and Goldstein, D. W. Allergy and the Cytologic Examination of Nasal Smears, *Arch Otolaryng* **16** 808 (Dec) 1932.

As the majority of the patients came to the clinic because of a history of a family history of sensitization, we are unable to furnish observations on as large a nonsensitized control series as we should like. Such a control necessitates a complete examination for sensitization. Accordingly, volunteers were few. However, a satisfactory control was secured in our group with infectious colds. Our observations may be classified as follows:

- 1 The cytology of the nasal smears of sensitized persons free from an infectious cold
  - (a) Sensitization to pollen alone (hay fever)
  - (b) Sensitization to pollen plus multiple food, epidermal and bacterial sensitization
  - (c) Multiple sensitization, but not to pollen
  - (d) Sensitization with an associated epidermal sensitization
- 2 The cytology of the nasal smears of sensitized persons during the period of an infectious cold
- 3 Comparative simultaneous differential counts of blood film and nasal film

TABLE 1—*Eosinophil Counts for Persons with Pure Hay Fever and No Other Sensitization Found by the Scratch Test*

Number of Patients	Type	Family History of Allergy	Percentage Variations in Cell Count of Nasal Smear			Percentage Variations in Blood Count					
			Polymorpho nuclears	Eosinophils	Monocytes	Polymorpho nuclears	Small Lym phocytes	Large Lym phocytes	Eosinophils	Monocytes	Basophils
8	Early	6	53.82	18.47	0	50.60	15.30	4.14	4.11	1.8	0
5	Late	5	37.77	23.63	0.1	56.60	19.24	6.13	4.11	3.5	0
6	Combined early and late	6	9.62	33.91	0.5	53.62	18.24	5.14	4.8	2.5	0
2	Potential	1	37.43	57.63	0	53.62	23.23	5.8	6.8	3.3	0.1
21	All types average	18	9.82	18.91	0.5	50.62	15.30	4.14	4.11	1.8	0.1

#### EOSINOPHIL COUNT IN NASAL SMEARS OF PATIENTS FREE FROM COLD

(a) *Sensitization to Pollen Alone (Hay Fever)*—In this group we included cases of hay fever in which no other allergy was found by the scratch test. There were 21 cases in this group (table 1). Had the patients been tested by the intradermal method doubtless other sensitizations would have been found in some of them. These cases represent 24 per cent of all the cases of hay fever observed in the preparation of this report (87). Accordingly, pure pollen sensitization is comparatively uncommon. The eosinophil cell count was between 18 and 40 per cent in 10 cases, between 42 and 68 per cent in 10 cases and 91 per cent in 1 case. The rest of the cell count was made up of polymor-

phonuclear cells In the smears in only 3 cases were mononuclear cells found In table 1 the data are arranged according to the type of hay fever

(b) *Sensitization to Pollen (Hay Fever) Plus Multiple Food, Epidermal and Bacterial*<sup>10</sup> Sensitization—In table 2<sup>11</sup> are the records of 66 patients with hay fever or potential hay fever (sensitization to pollen) associated with food, epidermal and bacterial sensitization, 45 of whom had seasonal hay fever and 21 of whom have no symptoms of hay fever but because they showed definite sensitization to pollen are classed as having potential hay fever For the entire group the eosinophil count in the nasal smears was between 19 and 40 per cent in 21 cases and between 41 and 91 per cent in 45 cases In the table

TABLE 2—*Eosinophil Counts for Patients with Hay Fever (Pollen) Plus Multiple Sensitization*

Num ber of Pa tients	Vari ation in Age, Years	Family History of Allergy, per Cent	Type of Hay Fever	Associated Sensitization				Count on Nasal Smear				Count on Blood Smear,	
								Polymor phonuclears		Eosino phils		Mono cytes, per Cent	Eosin ophils, per Cent
				Pol len	Food	Epi der mal	Bac terial	Num ber	Per Cent	Num ber	Per Cent		
8	16 31	50	Early, average	8	4	0	6	2	25 75	49	25 75	0	15 3
17	17 30	94	Late, average	17	17	12	5	48	14 81	52	19 86	0	211 42
20	16 32	90	Combined, aver- age	20	17	13	6	47	9 81	56	19 91	0	19 37
21	16 37	86	Potential, average	21	19	13	4	42	11 77	57	23 89	25*	116 34
66	16 37	80	Totals, average	66	57	38	21	47	9 81	54	19 91	0	116 4

\* This was the only instance in which a mononucleated lymphocyte like cell was noted

the counts are arranged in relation to the type of sensitization to hay fever, and no comment is required Mononucleated lymphocyte-like cells were seen in a smear in only 1 case

From the count in these two series it may be said that in definitely sensitized persons with an associated sensitization to pollen the nasal smears show an eosinophil count of 20 per cent or more (96.5 per cent of cases) Sixty-five and five-tenths per cent of all persons with sensitization to pollen had an eosinophil count of between 41 and 91 per cent

10 These tests were made with bacterial proteins furnished by the various manufacturers of food protein They are not disintegrated bacteria and act as bacterial vaccines

11 Reanalysis of cases included in the preliminary report<sup>12</sup> and the addition of others are responsible for the change in the percentages in this report

(c) *Multiple Sensitization But Not to Pollen*—Table 3 records the clinical data on 27 patients with multiple food, epidermal and so-called bacterial sensitization but without sensitization to pollen, as determined by the scratch test. The eosinophil cell counts in the nasal smears were between 25 and 40 per cent in 6 cases, between 41 and 60 per cent in 9 cases and between 61 and 89 per cent in 12 cases. It will be seen from these figures that 77.5 per cent of the patients had an eosinophil count between 41 and 89 per cent.

TABLE 3—*Eosinophil Counts for Patients with Multiple Sensitization But Not to Pollen*

Number of Patients	Variation in Age, Years	Family History of Allergy	Sensitization		Percentage Variations in Cell Count of Nasal Smear					Blood Eosinophils, per Cent	Complaints								
			Pollen	Food	Epidermal	Bacterial	Polymorpho-nuclears	Eosinophils	Mononuclears		Conjunctivitis	Dermatitis Venenata	Eczema	Gastro Intestinal Disturbance	Headache	Nasal Polyps	Rhinitis	Urticaria	Sinusitis
6	17-33	4	0	1	1	0	30-75	25-40	0	0.5	1			1	3		6	1	1
9	17-44	8	0	7	5	2	30-59	41-60	24* 26*	0.3			1	3	2		9	2	2
12	17-33	9	0	9	8	1	11-36	61-89	14* 25*	1-21†		1	1	5	3	1	11	3	4

\* In 2 cases only mononucleated cells were noted.

† Four per cent was noted in 1, 9 per cent in 1, 21 per cent in 2, and below 4 per cent in all the others.

(d) *Sensitization with an Associated Epidermal Sensitization*—Because of the striking hypersensitivity sometimes shown by persons with a reaction to epidermal proteins it was of interest to gather from series *a*, *b* and *c* the observations on those persons showing this type of sensitization and to compare the degree of increase in the eosinophil count in the nasal smears with those of patients who did not show epidermal sensitization. There were 50. Analysis shows the eosinophil count to be between 19 and 40 per cent in 11 cases, between 41 and 60 per cent in 13 cases and between 61 and 91 per cent in 26 cases.

A comparison shows

Percentage	Group	Eosinophil Count per Cent
23	Pure hay fever	41 to 91
23	Hay fever plus multiple sensitization, without epidermal allergy	41 to 91
44	No sensitization to pollen and no epidermal allergy	41 to 76
78	Epidermal allergy	41 to 91

From this analysis it seems that persons with epidermal sensitization have higher eosinophil counts in the nasal smears than those without epidermal sensitization.

# EOSINOPHIL COUNT IN NASAL SMEARS OF PATIENTS WITH AN INFECTIOUS COLD

We made observations on 140 persons with hay fever during the period of an infectious cold. The records of 80 of these are given in table 4, with data concerning the character of the sensitization. The records of 60 are given in table 5, in which the data are used for comparison. An analysis of the entire group shows that the eosinophil cell count in the nasal smear was between 0 and 20 per cent in 111 cases and between 21 and 32 per cent in 29 cases. This showed the great predominance of polymorphonuclears and indicated that there had been a reversal from the usual count in the nasal smears of such persons during the period of an allergic nasal disturbance. Eighty per cent of the patients with an infectious cold had an eosinophil count of 20 per

TABLE 4—*Observations on Sensitized Persons with an Infectious Cold*

Number of Patients	Variations in Age, Years	Family History of Allergy	Sensitization				Percentage Variations in Cell Count on Nasal Smear			Eosinophil Variation in Blood, per Cent
			Pollen	Food	Epi dermal	Bac terial	Poly morpho nuclears	Eosino phils	Mono cytes	
64	17-53	52	41	25	13	11	40-96*	4-20	1-45†	0-10‡
16	18-29	14	6	4	1	3	49-79	21-49	2-29§	1-4

\* The count was 90 per cent or higher in 15 cases

† This variation was encountered in only 21 cases

‡ The count was above 4 per cent in 13 cases

§ The count was 2, 26, 29, 14 and 15 per cent, respectively, in 5 cases

cent or less, and 68 per cent had an eosinophil count of 15 per cent or less.

In our preliminary report<sup>12</sup> we included only a few illustrative cases in which the reversal in the cell count was noted in the same person. Since that time we have kept records of 60 patients with hay fever (table 5) and 21 allergic patients without hay fever (table 6) for whom the cytologic picture of the nasal smear during a period of an infectious cold and a period of freedom from an infectious cold were recorded. The reversal was clearly demonstrated in all of them, and it was shown that an infectious cold in an allergic person may reduce the eosinophil count in the nasal smear far below that found in an allergic person free from a common cold.

12 Cowie, D. M., and Jimenez, B. The Value of Differential Cell Blood Counts on Nasal and Sputum Films in the Diagnosis of Conditions of the Upper Respiratory and Bronchial Tracts, *Am J Dis Child* 48:224 (July) 1934.

TABLE 5—*Eosinophil Counts on the Nasal Smears of Patients with Hay Fever During a Period of Freedom from Infectious Cold and a Period with Cold*

Case	Period Free from Cold		Period of Infectious Cold		Case	Period Free from Cold		Period of Infectious Cold	
	Poly-morpho-nuclears, per Cent	Eosino-phils, per Cent	Poly-morpho-nuclears, per Cent	Eosino-phils, per Cent		Poly-morpho-nuclears, per Cent	Eosino-phils, per Cent	Poly-morpho-nuclears, per Cent	Eosino-phils, per Cent
1	72	28	87	13	31	37	63	91	9
2	9	91	100	0	32	15	85	90	10
3	62	38	100	0	33	1	99	84	16
4	50	50	91	9	34	37	63	97	3
5	51	49	84	16	35	10	90	96	4
6	69	31	91	9	36	61	39	95	5
7	49	51	99	1	37	53	47	100	0
8	0	100	95	5	38	21	79	79	21
9	26	74	94	6	39	67	33	100	0
10	32	68	81	19	40	19	81	93	7
11	21	79	78	22	41	50	50	94	6
12	0	100	52	48	42	60	40	72	28
13	12	88	76	24	43	20	80	89	11
14	19	81	90	10	44	61	39	100	0
15	4	96	95	5	45	27	73	72	28
16	65	35	100	0	46	0	100	82	18
17	25	75	75	25	47	0	100	86	14
18	21	79	78	22	48	46	54	90	10
19	66	34	100	0	49	60	40	100	0
20	42	58	88	12	50	34	66	85	12
21	10	90	100	0	51	27	76	97	3
22	82	19	100	0	52	8	92	90	10
23	21	79	100	0	53	36	64	99	1
24	44	56	87	13	54	0	100	98	2
25	55	45	87	13	55	12	88	84	16
26	22	78	74	26	56	39	60	74	26
27	39	61	79	21	57	21	79	100	0
28	2	98	98	2	58	30	70	94	6
29	25	75	100	0	59	28	72	76	24
30	27	73	75	25	60	37	63	79	21

TABLE 6—*Eosinophil Counts on the Nasal Smears of Allergic Persons Not Sensitive to Pollen With and Without an Infectious Cold*

Case	Period Free from Cold		Period of Infectious Cold		Case	Period Free from Cold		Period of Infectious Cold	
	Poly-morpho-nuclears, per Cent	Eosino-phils, per Cent	Poly-morpho-nuclears, per Cent	Eosino-phils, per Cent		Poly-morpho-nuclears, per Cent	Eosino-phils, per Cent	Poly-morpho-nuclears, per Cent	Eosino-phils, per Cent
1	33	66	86	14	12	40	60	95	5
2	62	38	100	0	13	54	46	100	0
3	50	50	91	9	14	54	46	94	6
4	39	61	79	21	15	26	74	72	28
5	36	64	87	13	16	47	53	61	34*
6	62	38	78	22	17	22	64*	95	5
7	67	33	100	0	18	10	90	98	2
8	12	88	85	15	19	64	36	85	15
9	15	85	77	23	20	60	40	79	21
10	36	64	85	15	21	34	66	74	26
11	58	42	76	24					

\* The balance of the count was made up of other cells



COMPARATIVE SIMULTANEOUS DIFFERENTIAL COUNTS ON THE  
BLOOD AND NASAL FILMS

We were able to make simultaneous differential blood counts on 92 sensitized patients. These counts are analyzed in table 7 from data in tables 1, 2 and 3. This analysis indicates that 46 per cent had an eosinophil count in the blood of 4 per cent or above and 18 per cent,

TABLE 7—*Percentage of Eosinophil Cells in the Blood of Ninety-Two Sensitized Persons*

Percentage	0	1	2	3	4	5	6	7	8	9	10	11	16	21	23
Number of patients	6	10	16	17	16	8	2	5	4	3	1	1	1	1	1
Percentage of patients with percent ages of 4, 5, 6, 7 and more					46.7	29.3	20.6	18.5	13	8.5	5	4	3	2	1

a count of 7 per cent or above. The highest eosinophil count in the blood was 23 per cent (table 3), the patient had a 72 per cent eosinophil count in the nasal smear.

We have been unable to trace any definite relationship between the degree of eosinophilia in the blood and that in the nasal smear. For example

Cases	Eosinophils, Percentage	
	In Blood	In Nasal Smear
1	1	78
1	1	23
1	3	91
1	11	23
1	16	52
1	21	60
1	23	72

This study, however, does show that a considerable number of sensitized persons in whom we could find no parasitic cause for their allergy had a distinctly elevated eosinophil count in the blood. One of us (D. M. C.) has observed a patient for four years who has a persistent eosinophil count of between 7 and 11 per cent, with no other explanation than the determined allergy.

The well known clinical characteristics of allergic nasal mucous membrane have been frequently noted, but our observations lead us to believe that this is not a criterion on which a diagnosis must depend. In many cases of nasal disturbance in which this well known and valuable sign is not demonstrated the condition will be found to be on an allergic basis if systematic examinations of nasal smears are made. We should like to call attention to the discouragement that might easily follow first attempts at the use of this method. The cells must be clearly demonstrated. Masses of material staining red must be differentiated from nests of eosinophil cells, which are almost invariably mixed with polymorphonuclear cells or are found in the same neighborhood.

## CONCLUSIONS AND SUMMARY

1 Sensitized persons with a nasal discharge have a distinct increase in the eosinophil cells in the differential count of the nasal smear

2 It seems safe to say that an eosinophil count in a nasal smear of from 20 to 25 per cent indicates that the patient is allergic

3 Eosinophilia occurs in the nasal smears of persons with or without allergy for pollen. It seems to be more marked in persons who have an associated epidermal sensitization

4 During an infectious cold there is a reversal in the cytologic picture of the nasal smear of an allergic person. The eosinophil count may be reduced far below that ordinarily noted for an allergic person

5 Comparative simultaneous differential counts on the blood smear and nasal smear do not show a definite relationship to each other

6 Eosinophilia in the blood, sometimes of marked degree, is not uncommon in sensitized persons in whom no parasitic cause for the eosinophilia can be discovered, and this may be of long duration

7 The practical side to the making of differential counts on nasal smears is not inconsiderable. So-called common colds, particularly if they are recurrent, may have an allergic basis (eosinophilous colds). This can often be determined by studies of nasal smears, which may indicate whether or not a prolonged sensitization study is warranted

8 Boggy, pale nasal mucous membrane is not a reliable criterion for the diagnosis of allergic rhinitis. When present it is significant, but it is not always present

# RHEUMATIC CARDIAC DISEASE

## ASSOCIATION OF ACTIVE RHEUMATIC FEVER WITH HEART FAILURE

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The pathogenesis of heart failure in rheumatic cardiac disease is a subject of some controversy. The discussion centers about the influence of two general causes of failure: first, that of some infectious process, and second, that of a mechanical factor, exertional strain. Although clinical observations seem to indicate that the infectious element is decidedly the more important,<sup>1</sup> the exact nature of the infection has not been adequately determined. The present investigation was undertaken to clarify this point further.<sup>2</sup>

The clinical material reviewed for this study included 100 consecutive cases of uncomplicated rheumatic cardiac disease with heart failure, studied in the wards of the Presbyterian Hospital prior to 1932, 75 cases of rheumatic cardiac disease and heart failure with autopsy, and 50 clinical cases of syphilitic cardiac disease with decompensation. The history, results of physical and laboratory examination and postmortem observations have been studied to determine, if possible, the relative importance of the various factors associated with the onset of decompensation.

It has been found convenient to classify the clinical cases of rheumatic cardiac disease into three categories, depending on whether the disease was active, inactive or suspected to be active. The cases of syphilitic cardiac disease occurring in an approximately similar age group were employed as controls.

The protean nature of rheumatic fever<sup>3</sup> makes the determination of activity difficult. In this paper, rheumatic fever has been considered to be present when two or more of the following manifestations have

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1 (a) Lewis, T. Diseases of the Heart, New York, The Macmillan Company, 1933. (b) White, P. D. Heart Disease, New York, The Macmillan Company, 1931. (c) Burwell, C. S. The Progressive Nature of Cardiac Failure, *J A M A* **95** 1633 (Nov 29) 1930.

2 While this investigation was in progress, the following study appeared dealing with the same subject: Rothschild, M. A., Kugel, N. A., and Gross, Louis. Incidence and Significance of Active Infection in Cases of Rheumatic Cardiovascular Disease During Various Age Periods, *Am Heart J* **9** 586, 1934.

3 Boas, E. P., and Schwartz, S. P. Some Modes of Infection in Rheumatic Fever, *Am Heart J* **2** 375, 1927.

occurred arthritis, pains in the joints, subcutaneous nodules, development of a heart murmur under observations, rheumatic pleurisy, pneumonia, and pericarditis, and certain cutaneous eruptions Table 1 lists the frequency of the occurrence of these manifestations, with records of temperature, leukocytosis and response to salicylates incorporated The specificity of these criteria has been extensively discussed in the literature<sup>4</sup> In several instances, the presence of rheumatic activity seemed to be established simply by electrocardiographic evidence, without the presence of any of the other manifestations already mentioned This is in accord with current belief<sup>5</sup>

TABLE 1—*Percentage Incidence of Rheumatic Manifestations in 144 Admissions of 100 Patients with Rheumatic Fever and in 70 Admissions of 50 Patients with Syphilis*

Manifestation	Rheumatic Fever						Syphilis	
	Active		Suspected		Inactive			
	Per Cent	Num ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num ber
Electrocardiographic changes*	24	34	4	5			25	18
Rheumatic fever before admission	11	17	<1	1				
Subcutaneous nodules	<1	1						
Arthritis	7	10	1	2				
Development of heart murmur	7	10	4	6				
Pericardial friction rub	13	18	1	1			4	3
Pleural friction rub	7	10	1	2			4	3
Transient pneumonia	4	5						
Active lesions at postmortem examination	9	13	1†	2†				
Chorea (?)			<1	1				
Miscellaneous	2	3	5	7				
Leukocyte count more than 11,000 per cubic milli- meter of blood	32	47	15	21	Not recorded		60	42
Temperature more than 100 F (rectal)	32	47	13	19			26	18
Response to salicylates	21	30	4	5			0	0

\* Prolongation of the PR interval and also intraventricular block

† Only one active focus one year after admission

In this series, in a number of cases in which the disease was considered active, the patient did not present clinically the necessary criteria just listed These have been classified as instances of "suspected" active

4 (a) Coburn, A Rheumatic Infection and the Rheumatic State, Baltimore, Williams and Wilkins Company, 1932 (b) Rolly, F Der akute Gelenkrheumatismus, Berlin, Julius Springer, 1920 (c) Paul, J R Pleural and Pulmonary Lesions in Rheumatic Fever, *Medicine* **7** 383, 1928 (d) Clawson, B I The Aschoff Nodule, *Arch Path* **8** 664 (Oct) 1929

5 Peabody, F W Heart-Block Associated with Infectious Diseases, *Arch Int Med* **5** 252 (March) 1910 Parkinson, J, Gosse, A H, and Gunson, E B Heart and Its Rhythms in Acute Rheumatism, *Quart J Med* **13** 363, 1920 Cohn, A E, and Swift, H F Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J Exper Med* **39** 1, 1924 Levy, R, and Turner, K Impaired Auriculoventricular Conduction in Rheumatic Fever, *Arch Int Med* **43** 267 (Feb) 1929 Oppenheimer, B, and Rothschild, Marcus A Electrocardiographic Changes Associated with Myocardial Changes, *J A M A* **69** 429 (April 11) 1917

rheumatic fever For example, a transient friction rub over the precordium without other confirmatory signs led one to suspect active rheumatic cardiac disease but did not establish its presence (table 1) In many cases, no evidence of active rheumatic fever could be found In most of these cases, in fact, there was no clue to any factor associated with decompensation While the patients with syphilis were free from active rheumatic fever, it is of interest that several of the manifestations of rheumatic fever appeared, such as electrocardiographic changes, transient friction rub, etc (table 1) The complete clinical picture, however, prevented any confusion with rheumatic fever<sup>6</sup>

The age group represented by the patients with rheumatic fever ranged from 5 to 69, with a median age of 31 The patients with syphilis were between the ages of 26 and 71, with a median age of 46

TABLE 2—Percentage Incidence of Mechanical Factors in 144 Admissions of 100 Patients with Rheumatic Fever and in 70 Admissions of 50 Patients with Syphilis

Factor	Rheumatic Fever						Syphilis	
	Active		Suspected		Inactive			
	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number
Exercise or work	<1?	1?	<1	1	1	2	4*	3*
"Worry"	1	2			<1	1	3*	2*
Pregnancy					5	7		
Cessation of digitalis					<1	1		
Convulsions					<1	1		
"Asthma"							1	1
Aneurysm							3	2

\*The common cold was also present

The sex distribution was unequal, females preponderating in the series with rheumatic fever and males in that with syphilis The incidence of active rheumatic fever seemed slightly higher in the younger age groups

In the series of clinical cases of rheumatic cardiac disease with decompensation active rheumatic fever was demonstrable in 45 per cent In 34 per cent there was no evidence of an active process The remaining 21 per cent were suspected of being instances of active rheumatic fever, according to the aforementioned criteria The combined group of cases of active and suspected active rheumatic fever comprised 66 per cent of the entire series Some mechanical strain, such as exertion, pregnancy, etc (table 2), as the sole factor associated with decompensation was found in only 8 per cent of the cases No significant factor could be found in 26 per cent In the series of patients who came to autopsy the percentages correspond to those for the patients not coming

6 Juster, I R, and Pardee, H E B Abnormal Electrocardiograms in Patients with Syphilitic Aortitis, *Am Heart J* 5 85, 1929 Coombs, C F Syphilis of the Heart and Great Vessels, *Lancet* 2 227, 281 and 333, 1930

to autopsy Sixty-six per cent of the patients showed macroscopic and microscopic changes indicative of active rheumatic fever

A high incidence of infection of the upper respiratory tract was found in the cases of rheumatic cardiac disease In fact, this type of infection was the only factor of importance, other than active rheumatism, found accompanying heart failure in 45 per cent of these cases Table 3 shows the percentage incidence of the common cold, bronchitis, etc There was a similar magnitude of incidence of this type of infection in the cases of syphilitic cardiac disease, making it difficult to determine the exact rôle of this factor This point will be considered later in the article

The results in the cases of syphilitic cardiac disease were as follows In 7 per cent there was a mechanical factor, in 45 per cent, no obvious

TABLE 3—*Percentage Incidence of Infection of Respiratory Tract in 144 Admissions of 100 Patients with Rheumatic Fever and in 70 Admissions of 50 Patients with Syphilis*

Infection	Rheumatic Fever						Syphilis	
	Active		Suspected		Inactive			
	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber
Common cold	13	18	5	7	5	7	24	17
"Grip"			<1	1				
Bronchitis	<1	1	6	8			3	2
"Cough" prior to decompensation	5	7	4	6	<1	1	13	9
"Cough" following decompensation	4	6	1	2	2	3	10	7
Chronic tonsillitis			2	3				
"Sore throat" *	17	25	<1 (?)	4				
Pneumonia					<1	1	1	1

\*Preceding the onset of an acute rheumatic episode

factor, and in the remaining 48 per cent, an infectious element, which in this series was an infection of the upper respiratory tract

#### COMMENT

The results of this study indicate a significant relationship between active rheumatic fever and heart failure in patients with rheumatic cardiac disease Under these circumstances, the remarkable recovery and the prolonged period of well-being after decompensation of severe degree in patients with rheumatic cardiac disease becomes understandable Furthermore, presuming that an infection of the upper respiratory tract introduces active rheumatism, one is able to comprehend "button-hole" mitral stenosis perfectly compensated for even in strenuous activity until, for example, a common cold is contracted, at which point heart failure suddenly sets in <sup>7</sup>

<sup>7</sup> Scarlett, E P The Significance of Infection in Cardio-Vascular Disease, Canad M A J 26 562, 1932

Similarly, the greatest number of patients with rheumatic cardiac disease and decompensation are admitted to the hospital at the peaks of incidence of rheumatic fever in New York City <sup>4a</sup> The significance of this observation, however, must be tested by a larger series of observations

The exact rôle that infection in the upper respiratory tract plays in decompensation is a topic for speculation The equal frequency of occurrence of such infection in both patients with rheumatism and those with syphilis makes one wonder which came first, the infection or the decompensation The omission of definite statements in respect to this

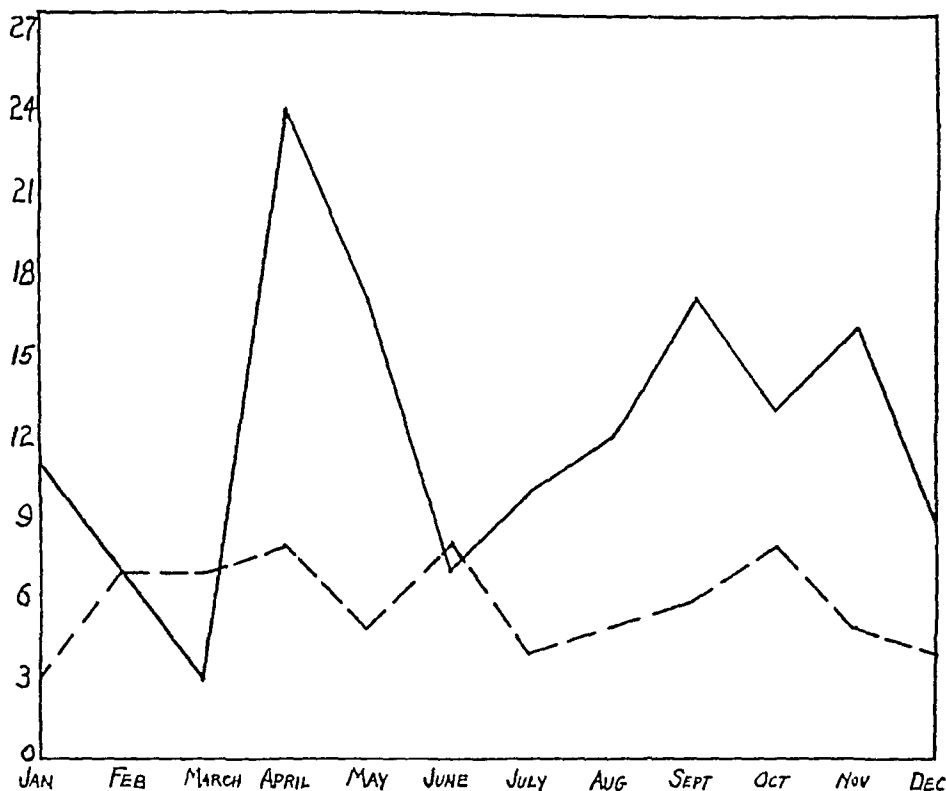


Chart showing the incidence of decompensation in 144 admissions of 100 patients with rheumatic fever and in 70 admissions of 50 patients with syphilis The figures at the left indicate the number of admissions The black line indicates the patients with rheumatic fever, and the broken line, the patients with syphilis

point in the cases reported and the insidious onset of the symptoms of decompensation in the vast majority of cases preclude any definite estimate of relationships in regard to time But the importance of infection in the upper respiratory tract as a factor in producing decompensation is understandable if one considers such infection as introducing active rheumatic fever <sup>8</sup> There is, however, no myocardial process with

<sup>8</sup> Boas and Schwartz <sup>3</sup> Coburn <sup>4a</sup> Branson, W P S Avenues of Rheumatic Infection, Brit M J 2 1429, 1912 McCulloch, H, and Irvine-Jones, E The Rôle of Infection in Rheumatic Children, Am J Dis Child 37 252 (Feb) 1929

which the infection of the respiratory tract can be correlated in syphilitic cardiac disease. Thus, while the incidence of this type of infection is approximately equal in patients with syphilis and those with rheumatic fever, the occurrence of such an infection must have a different significance in the two groups.

The importance of infection in general in producing decompensation is not new to the literature. Lewis<sup>1a</sup> only recently again condemned the overemphasis of older views on the effect of strain in the production of heart failure (as opposed to infection). White<sup>1b</sup> upheld the importance of the mechanical element, claiming that the pendulum is swinging too far toward the infectious side. Burwell<sup>1c</sup> found that "neither the severity nor duration of overwork corresponds with the degree or time of onset of failure." The bulk of recent published opinion agrees with the latter view. In respect to the cases of rheumatism, the present study supports the opinion that it is not only infection but a specific active rheumatic infection that is the important factor in the production of heart failure.

#### SUMMARY

A study has been made of 100 consecutive cases of rheumatic cardiac disease with heart failure studied in wards, of 75 cases of the same condition with autopsy, and of 50 cases of syphilitic cardiac disease included for comparative purposes.

Signs of active rheumatic fever have been demonstrated in 45 per cent of the clinical cases of rheumatic cardiac disease. Activity has been suspected in an additional 21 per cent.

In the pathologic material, active lesions have been found in 66 per cent of the cases of rheumatic cardiac disease.

An exertional or mechanical factor associated with cardiac insufficiency was definite in only 8 per cent of the cases of rheumatic cardiac disease and 7 per cent of the cases of syphilitic cardiac disease. There was no demonstrable factor in the remaining 26 per cent and 48 per cent of the cases of rheumatic and syphilitic cardiac disease, respectively.

Infection of the respiratory tract is concomitant with the loss of cardiac reserve in 50 per cent of the clinical cases of rheumatic and syphilitic cardiac disease.

A seasonal rise in the number of patients with rheumatic fever admitted to the hospital for cardiac insufficiency is indicated, corresponding to the known statistics on morbidity for rheumatic fever in New York City. The finding is not demonstrable in the series with syphilitic cardiac disease.



# CLINICAL STUDIES OF RESPIRATION

## V RELATION OF DYSPNEA AND AIR HUNGER TO CHANGES OF THE EXPIRATORY VOLUME OF THE CHEST

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AND

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The cause of cardiac dyspnea and air hunger is still disputed. The fact that it cannot be explained simply by alteration of the carbon dioxide and oxygen content of the blood<sup>1</sup> opens the way for renewed investigation of other respiratory factors.

Greene and Coggeshall<sup>2</sup> showed that increases in the expiratory position of the chest take place in normal subjects during muscular work and while basal metabolism is being measured. Two of their subjects who manifested such an increase also experienced shortness of breath, but when one of us (J A G)<sup>3</sup> exposed normal subjects to high concentrations of carbon dioxide and low concentrations of oxygen, both simultaneously and separately, a constant increase in the expiratory position of the chest did not occur. In these experiments precautions were taken to reduce psychic factors to a minimum.<sup>2</sup>

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From the Department of Internal Medicine, State University of Iowa Medical School

1 (a) Peters, J P, and Barr, D P. The Carbon Dioxide Absorption Curve and the Carbon Dioxide Tension of the Blood in Cardiac Dyspnea, *J Biol Chem* **45** 537 (Feb) 1921. (b) Eppinger, H, Kisch, F, and Schwarz, H. Das Versagen des Kreislaufes, Berlin, Julius Springer, 1927, p 43. (c) Fraser, F R, Harris, C F, Hilton, R, and Linder, G C. Arterial Carbon Dioxide Pressure in Cardiac Dyspnea, *Quart J Med* **22** 1 (Oct) 1928. (d) Cullen, G E, Harrison, T R, Calhoun, J A, Wilkins, W E, and Tims, M M. Studies in Congestive Heart Failure. XIII The Relation of Dyspnea of Exertion to the O<sub>2</sub> Saturation and Acid-Base Condition of the Blood, *J Clin Investigation* **10** 807 (Oct) 1931.

2 Greene, J A, and Coggeshall, H C. Clinical Studies of Respiration I Plethysmographic Study of Quiet Breathing and of Some Ordinary Activities on the Expiratory Position of the Chest in Man, *Arch Int Med* **52** 44 (July) 1933, II Influence of Determination of Basal Metabolism on Respiratory Movements and Effect of These Alterations on Calculated Basal Metabolic Rate, *ibid* **52** 226 (Aug) 1933.

3 Greene, J A. Clinical Studies of Respiration III Influence on the Expiratory Position of the Chest in Man of an Inspired Air Which Is Low in Oxygen and High in Carbon Dioxide and of Resistance to Inspiration and to Expiration, *Arch Int Med* **52** 447 (Sept) 1933.

The purpose of the present investigation was to study the effect of excess of carbon dioxide and deficiency of oxygen in patients with cardiac disease, particularly with reference to the expiratory position of the chest, and to ascertain whether or not there is any relationship between an increase in the expiratory position of the chest and air hunger and dyspnea

#### METHOD

The method of altering the composition of the inspired air and obtaining simultaneous spiograms and plethysmograms was the same as that previously employed<sup>3</sup> It is a procedure which reduces psychic factors to a minimum The Haldane method of analysis of gas was used In each case preliminary observations were made to accustom the patient to the procedure

Of the twenty patients studied, there were four with neurocirculatory asthenia, one with pernicious anemia, two with extracardial murmurs and thirteen with organic cardiac disease The last group included two without heart failure, six with slight congestive failure and five with advanced congestive failure Five of the twenty patients had orthopnea, and nine experienced dyspnea on slight exertion

#### RESULTS

The sensitivity of seventeen of the patients to alteration in the composition of the inspired air was within the limits designated as normal by Schneider and Treusdell,<sup>4</sup> Peabody<sup>5</sup> and Greene<sup>3</sup> The carbon dioxide content of the inspired air varied from 4.2 to 10.4 per cent, and the oxygen content, from 5.6 to 10.3 per cent The simultaneous excess of carbon dioxide and deficiency of oxygen ranged from 4.9 and 12.8 per cent to 7.5 and 9.1 per cent, respectively Patient 14 (table 1) was abnormally sensitive, he did not experience discomfort during control periods but became short of breath when the concentration of carbon dioxide was increased to 4 and 4.5 per cent and when that of oxygen was decreased to 14.7 and 14 per cent The result in the case of patient 17 (table 1), who was suffering from advanced congestive failure, was open to criticism, his discomfort was the same in both the control and the test period The patient with pernicious anemia, patient 1 (table 1), became very short of breath when the content of oxygen was reduced to 11 per cent

Table 2 shows that expiratory enlargement of the chest occurred<sup>1a</sup> in less than one fourth of the experiments on normal subjects,<sup>1b</sup> in

4 Schneider, E. C., and Treusdell, D. A Study of Low Oxygen Effects During Re-Breathing, *Am J Physiol* **55** 223 (March) 1921, The Effects on the Circulation and Respirations of an Increase in Carbon Dioxide Content of the Blood in Man, *ibid* **63** 155 (Dec.) 1922

5 Peabody, F. W. Clinical Studies of Respiration. I. The Effect of Carbon Dioxide in the Inspired Air on Patients with Cardiac Disease, *Arch Int Med* **16**:846 (Nov.) 1915

BLA

TABLE 1—*Reaction of Twenty Patients to Alterations in the Composition of Inspired Air*

Patient	Diagnosis	Carbon Dioxide			Oxygen			Carbon Dioxide and Oxygen		
		Per centage	Air Hunger	Expiratory Position	Per centage	Air Hunger	Expiratory Position of Chest	Percentage Carbon Dioxide	Per centage Oxygen	Expiratory Position
1	Pernicious anemia, dyspnea on exertion	44	0	No change	11.1	Marked	Moderate increase	45	14.8	Slight
2	Extracardiac murmur	52	0	Slight increase	63	0	No change			
3	Extracardiac murmur	59	0	Moderate	56	0	Slight			
4	Neurocirculatory asthenia, palpitation	51	0	No change	80	0	No change			
5	Neurocirculatory asthenia, palpitation	61	Slight	Very slight	62	Slight	Very slight			
6	Neurocirculatory asthenia, dyspnea on exertion	72	Marked	Marked	69	Marked	Marked			
7	Neurocirculatory asthenia, dyspnea on exertion	66	Marked	Marked	99	Marked	Marked			
8	Mitral and aortic stenosis (rheumatic) without heart failure	55	Moderate	Moderate	71	Marked	Very slight			
9	Congenital cardiac disease without failure	57	0	No change	78	0	Slight	68	9.8	No change
10	Mitral stenosis (rheumatic), dyspnea on exertion	58	0	No change	98	0	No change			
11	Arteriosclerosis, dyspnea on exertion	60	0	Moderate	69	Moderate	Marked			
12	Arteriosclerosis, dyspnea on exertion	60	0	Moderate	79	0	No change			
13	Aortic stenosis, rheumatic, dyspnea on exertion	55	0	Moderate	59	0	Slight			
14	Mitral stenosis, rheumatic, dyspnea on exertion	53	0	Slight	76	0	No change			
15	Hyperthyroidism, dyspnea on exertion	40	Marked	Marked	147	Marked	Marked			
16	Arteriosclerosis, orthopnea	45	Marked	Marked	140	Marked	No change	50	18.0	Marked
17	Arteriosclerosis, orthopnea, Cheyne Stokes respiration	50	0	No change	87	0	No change			
18	Arteriosclerosis, orthopnea, Cheyne Stokes respiration	54	0	Very slight	141	Moderate	No change			
19	Arteriosclerosis, slight orthopnea	40	?	Slight	69	?	Very slight			
20	Arteriosclerosis, slight orthopnea	50	0	No change	100	?	Slight			
		42	0	Moderate	96	0	Moderate			
		104	Slight	Moderate to marked	103	0	Moderate	75	9.1	Marked
		58	0	Moderate	84	0	No change	49	12.8	No change

one half of the experiments on the various patients,<sup>1c</sup> simultaneously with air hunger more frequently in the patients with mild cardiac failure and neurocirculatory asthenia than in those with severe congestive failure<sup>1d</sup> and more frequently in patients who suffered from dyspnea on exertion than in other patients or in normal subjects. Of the fourteen patients with dyspnea on exertion, ten increased the expiratory position to a significant degree, of the six other patients only one, and of the twenty-one normal subjects only five, increased the expiratory position appreciably.

Shortness of breath without an increase of the expiratory position occurred in two instances. Patient 15 (table 1) did not experience air hunger when the content of oxygen was reduced to 8.7 per cent, but when the experiment was repeated thirty minutes later with a concentration of oxygen of 14.1 per cent she complained of shortness of breath.

TABLE 2—*Expiratory Enlargement of the Chest in Normal Subjects and Patients*

Diagnosis	Number of Tests	Number of Instances of Increased Expiratory Position	Number of Instances of Air Hunger
Normal condition	21	5	
Pathologic condition			
Pernicious anemia	3	1	2
Neurocirculatory asthenia	10	5	6
Cardiac disease			
Without failure	4	0	
With slight failure	16	9	6
With severe failure	14	7	1
Total	68	27	15

This inconsistency, together with the fact that the rate and depth of the patient's breathing increased only slightly and that she did not appear in the least short of breath, throws much doubt on the validity of the experiment. The second instance occurred in a patient with neurocirculatory asthenia, patient 7 (table 1), who appeared to be dyspneic. Just as the mouthpiece and nose-clip were being applied the patient increased the expiratory position of his chest greatly and maintained it with a slight additional increase throughout the experiment.

Definite dyspnea occurred in only five patients (table 1, patients 1, 6, 7, 14 and 19). Patients 6, 7 and 14 (table 1) exhibited dyspnea in all tests, while it occurred in patient 1 (table 1) only with a lack of oxygen and in patient 19 (table 1) only with an excess of carbon dioxide. A marked enlargement of the expiratory volume of the chest occurred in only two patients without dyspnea (table 1, patients 10 and 19). Dyspnea was accompanied by moderate air hunger in patient 10 (table 1) and was not associated with air hunger in patient 19 (table 1).

## COMMENT

The variations in the sensitivity of our patients to an excess of carbon dioxide and a deficiency of oxygen compare favorably with those observed in normal subjects by Schneider and Treusdell<sup>4</sup> and Peabody<sup>5</sup>. That this variation in susceptibility is unrelated to the degree of heart failure is illustrated by the fact that patient 19 (table 1), who suffered from severe congestive failure, experienced only slight air hunger with mild dyspnea when the alveolar carbon dioxide tension was increased to 104 per cent by rebreathing. These results tend to confirm the conclusions of other investigators that anoxemia and acidosis caused by carbon dioxide are not the major factors in cardiac dyspnea.

If shortness of breath in cardiac disease is due partly to a reduction in vital capacity, as Peabody and Wentworth<sup>6</sup> and others have shown, and if an increase in the expiratory position of the chest necessarily effects a further reduction in vital capacity, it is difficult to understand why the patients with severe cardiac failure did not experience severe air hunger when the increase in expiratory position occurred, except by assuming that they were relatively insensitive to high concentrations of carbon dioxide and to low concentrations of oxygen.

The similarity of response of patients with neurocirculatory asthenia and mild heart failure suggests that in both instances the shortness of breath was produced by a reflex mechanism comparable to that which Harrison and his collaborators<sup>7</sup> demonstrated in their experimental study of cardiac dyspnea. The psychic factor no doubt plays a rôle in the production of dyspnea in some persons. The discovery by Levine and Wilson,<sup>8</sup> White<sup>9</sup> and Flack<sup>10</sup> that the vital capacity is diminished in the effort syndrome and shell shock and in aviators under "flying strain" suggests that some factor other than a mechanical one (perhaps an increase in the expiratory position of the chest) may play a rôle in the respiratory symptoms in such cases. In our patients with neurocirculatory asthenia, whose predominating symptom was shortness of breath, there was an increase in the position of the chest every time an unusual demand was made on the respiratory apparatus. This sug-

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6 Peabody, F. W., and Wentworth, J. A. Clinical Studies of Respiration. IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, *Arch. Int. Med.* **20**: 443 (Sept.) 1917.

7 Harrison, T. R., Harrison, W. G., Calhoun, J. A., and Marsh, J. P. Congestive Heart Failure. XVII. The Mechanism of Dyspnea on Exertion, *Arch. Int. Med.* **50**: 690 (Nov.) 1932.

8 Levine, S. A., and Wilson, F. N. Observations on the Vital Capacity of the Lungs in Cases of "Irritable Heart," *Heart* **7**: 53 (July) 1919.

9 White, P. D. Observations on Some Tests of Physical Fitness, *Am. J. M. Sc.* **159**: 866 (June) 1920.

10 Flack, M. The Respiratory Efficiency in Relation to Health and Disease, *Lancet* **2**: 593 (Sept. 17), 637 (Sept. 24), 693 (Oct. 1) 1921.

gests that the interrelationship of the inspiratory and expiratory phases was disturbed either because of an increase in the depth of inspiration or because of a decrease in the extent of expiration. In their patients White<sup>9</sup> and Flack<sup>10</sup> found the available active expiratory power and ability to hold the breath to be reduced about 50 per cent. Observations of this kind lend plausibility to Lumsden's<sup>11</sup> findings that there are separate centers in the midbrain for inspiration and expiration.

Direct evidence that alterations in the expiratory or resting position of the chest are of reflex origin is to be found in the observation of Barcroft and Verzar<sup>12</sup> that an increase in the expiratory position occurs during the rigor produced by exposure to cold. They attributed the increase to summation of inspirations but made no mention of air hunger or dyspnea.

#### SUMMARY

Under conditions designed to reduce psychic influences to a minimum, the effect of raising the carbon dioxide content and lowering the oxygen content of the inspired air was studied by means of simultaneous spiograms and plethysmograms of twenty patients, thirteen of whom had organic cardiac disease, nine dyspnea on exertion and five orthopnea.

No correlation between sensitivity to such alterations in the composition of the inspired air and the degree of heart failure were discovered.

An increase in the expiratory position of the chest occurred more frequently in patients who suffered from shortness of breath on exertion than in other patients or in normal subjects.

Two thirds of the patients in whom the expiratory position of the chest increased manifested air hunger.

Definite air hunger did not occur without simultaneous increase of the expiratory position of the chest.

Definite dyspnea occurred in five patients, all of whom exhibited moderate or marked enlargement of the expiratory volume of the chest. Dyspnea did not occur in two patients with marked elevation of the expiratory level of the chest.

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11 Lumsden, T. Observations on the Respiratory Centers in the Cat, *J Physiol* **57** 153 (March) 1923, Observations on the Respiratory Centers, *ibid* **57** 354 (Aug) 1923.

12 Barcroft, J, and Verzar, F. The Effect of Exposure to Cold on the Pulse Rate and Respirations of Man, *J Physiol* **71** 373 (April) 1931.

# CARBOHYDRATE INTOLERANCE AND INTESTINAL FLORA

## II BACTERIOLOGIC STUDIES OF THE FECAL FLORA

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In another paper<sup>1</sup> a clinical study of sixty cases of a condition designated as intestinal intolerance of carbohydrate will be reported. This clinical syndrome characterized by flatulence, abdominal pain and belching was first described by Schmidt and Strasburger.<sup>2</sup> Herter<sup>3</sup> and Kendall<sup>4</sup> stated that this condition was probably due to the presence of excessive numbers of *Clostridium Welchii* in the intestine. Hurst and Knott<sup>5</sup> stated the belief that variations in the intestinal flora were not the cause of this syndrome but the result of an excess of carbohydrate in the colon due to an insufficiency of ferments.

In the present investigation, fecal specimens from persons suffering from intolerance of carbohydrate were studied bacteriologically. The study was directed primarily toward quantitative and qualitative tests for *C. Welchii*. Attempts were made to determine the diagnostic value of some of the methods suggested for routine use in the clinical laboratory.

### EXPERIMENTAL METHODS

Fecal specimens were examined within three hours after collection. After mixing them to obtain a representative sample, 1 Gm of fecal material was weighed out, carefully emulsified in 10 cc of sterile water and diluted so that each cubic centimeter of the suspension contained 0.01 Gm of the original material. Liquid stools were standardized to the same turbidity as that of the weighed preparation. It is, of course, apparent that this method of preparing a "standard" suspension

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1 Althausen, T L, Gunnison, J B, Marshall, M S, and Shipman, S J. *Arch Int Med*, to be published

2 Schmidt, A, and Strasburger, J. *Experimentelle und klinische Untersuchungen über Funktionsprüfung des Darmes VI Ueber die intestinale Gahrungsdyspepsie der Erwachsenen*, *Deutsches Arch f klin Med* **69** 570, 1901

3 Herter, C A. The Influence of Food and of Epithelial Atrophy on the Manifestations of Saccharo-Butyric Intestinal Putrefaction, *J A M A* **49** 1965 (Dec 14), 2077 (Dec 21) 1907

4 Kendall, A I. Intestinal Intolerance for Carbohydrate, Associated with Overgrowth of Gas Bacillus (*Bacillus Welchii*), *J A M A* **86** 737 (March 11) 1926

5 Hurst, A F, and Knott, F A. *Quart J Med* **24** 171, 1931

is inaccurate because of differences in water content of specimens as well as for other reasons. However, comparisons of the turbidity of a large series of such suspensions showed little variation, and no significance was attached to slight differences in results. Thus it was felt that this method was adequate for the purpose.

For quantitative estimation of *Cl. Welchii*, dextrose agar containing ferric chloride and sodium sulphite was prepared according to the formula of Wilson and Blair<sup>6</sup>. One cubic centimeter amounts of tenfold serial dilutions of fecal material of from 1/10 to 1/10,000 were plated in this medium. The plates were incubated in phosphorus jars as described by Varney<sup>7</sup>. Chapman<sup>8</sup> found a certain degree of selective action for *Cl. Welchii* with this method of obtaining anaerobiosis. The colonies were counted after twenty-four hours of incubation at 37 °C. The counts were checked in some instances by plating measured amounts of suspension on dextrose blood agar plates<sup>8</sup>.

As a qualitative test for the presence of *Cl. Welchii*, the "stormy fermentation" of sterile milk in Smith tubes was used<sup>9</sup>. The standard inoculum was 1 cc of the stock dilution, i. e., 0.01 Gm of fecal material. Two tubes were inoculated from each specimen, one with unheated material and the other with a portion which had been heated at 80 °C for ten minutes. After twenty-four hours' incubation at 37 °C the nature of the curd, the proportion of whey expressed and the approximate amount of gas evolved were recorded.

Actual isolation and identification of *Cl. Welchii* were accomplished either from ferric chloride-sodium sulphite agar plates used for counts or from heated tubes of milk showing stormy fermentation. This was done by streaking the material on blood agar plates containing 2 per cent dextrose and 20 per cent blood which were incubated in phosphorus jars for forty-eight hours. Colonies of *Cl. Welchii* showed characteristic olive green coloration and were surrounded by a zone of hemolysis and chocolate brown precipitation as described by Zeissler<sup>10</sup>. The colonies were streaked again on blood plates, fished to beef heart and finally reisolated by the shake method in liver agar deeps. The type of *Cl. Welchii* according to Simonds<sup>11</sup> classification was determined by fermentation tests of glycerin and inulin.

Qualitative tests for the presence of aciduric organisms were made according to the method used by Morris, Porter and Meyer<sup>12</sup>. Acetic acid was added to an extract broth containing 1 per cent dextrose so as to yield a final concentration of fifth-normal, tenth-normal and twentieth-normal acid, respectively. A tube of each concentration was inoculated with 1 cc of the stock dilution of feces, incubated for ten days and observed for growth. Quantitative estimations of aciduric organisms were also carried out. Serial dilutions were plated in whey agar at *pH* 5.6, and counts were made after forty-eight hours of incubation.

6 Wilson, W. J., and Blair, E. M. M. *J. Hyg.* **24**:111, 1925.

7 Varney, P. L. *J. Lab. & Clin. Med.* **11**:1183 (Sept.) 1926.

8 Chapman, G. H. *J. Bact.* **16**:49, 1928.

9 Herter, C. A. On Bacterial Processes in the Intestinal Tract in Some Cases of Advanced Anemia, with Especial Reference to Infection with *B. Aerogenes Capsulatus* (*B. Welchii*), *J. Biol. Chem.* **2**:1, 1906.

10 Zeissler, J. Die Gasodeminfectionen des Menschen, in Kolle, W., and Wassermann, F. *Handbuch der pathogenen Mikroorganismen*, Jena, Gustav Fischer, 1928, vol. 4, pt. 2, chap. 14, p. 1099.

11 Simonds, J. P. Studies in *Bacillus Welchii* with Special Reference to Classification and to Its Relation to Diarrhea, Monogr. 5, Rockefeller Institute for Medical Research, Sept. 27, 1915.

12 Morris, G. B., Porter, R. L., and Meyer, K. F. *J. Infect. Dis.* **25**:349, 1919.



To test for the proteolytic activities of the flora, 1 cc of serial dilutions of the unheated specimen of from 1 100 to 1 10,000,000 were inoculated into freshly boiled peptic digest beef heart medium and incubated for two weeks. Darkening and disintegration of the meat accompanied by the production of foul gas were considered to be evidence of proteolysis.

Tubes containing sterile potato mash (one part potato to six parts water) were inoculated in the same manner as the tubes containing beef heart to test the fermentative action on this substance. In addition, from 0.1 cc to 1 cc of potato mash was added to 10 per cent suspensions of feces. The relative amount of gas produced was recorded after twenty-four hours of incubation at 37 C.

Fecal specimens from fifty persons who presented a clinical picture of intolerance of carbohydrate were studied. Twenty-four of these persons showed typical symptoms and had no other intestinal disease, three suffered from other intestinal disorders as well, and twenty-three had symptoms suggestive of this condition but in milder form than the typical cases. It is unfortunate that only one specimen was obtained from a number of patients. However, in a series of twelve cases weekly specimens were studied over a period of from one to four months, and in two instances tests were made daily for a week. Some samples were taken during the characteristic exacerbations, others were tested during various periods of the dietary regimen<sup>1</sup>. As controls, seven specimens were examined from persons suffering from other intestinal diseases, three from persons with hypochromic anemia and fourteen from normal persons.

The majority of the specimens were normal in gross appearance. As a rule, they were formed and dark in color, although in ten cases they were light-colored and unformed and contained bubbles of gas. Liquid stools were submitted in only seven instances. Mucus was present in the feces of twelve patients, all of whom had severe symptoms and were refractory to treatment. Except in the cases in which mucus was found in the feces, there was no correlation of the nature of the stool either with the severity of the symptoms or with the bacteriologic findings.

## RESULTS

The results of the various tests for *Cl. Welchii* are summarized in table 1. The detailed analyses of twenty-one<sub>4</sub> specimens chosen at random are given in table 2.

*Number of the Organisms Present*—It was felt that the method of quantitative estimation of *Cl. Welchii* gave a reasonably accurate indication of the actual number of the organisms present in the feces both in vegetative and in spore states. In ferric chloride-sodium sulphite agar colonies of *Cl. Welchii* were surrounded by a wide jet black zone. Although a number of other organisms produce such colonies, repeated studies of an extensive series of black colonies showed them to be *Cl. Welchii* with only a few exceptions. No other species of *Clostridium* which reduced sulphite was encountered in this series by the method used. Occasionally a streptococcus was found which formed minute black colonies readily distinguishable from *Cl. Welchii*. There was close agreement with counts obtained by plating on dextrose agar plates.

The counts ranged from less than 100 to as high as 250,000,000 sulphite-reducing organisms per gram of feces. Of specimens from

fourteen normal persons, three gave counts lower than 1 000, and none had a count higher than 10,000,000 organisms per gram. For eight of forty-four patients with intolerance of carbohydrate tested the counts were less than 1,000, but in eight instances they exceeded 10 000 000 organisms per gram. With the exception of this group of eight persons with counts exceeding 10,000,000 per gram, there was no evidence that the feces of those unable to tolerate carbohydrate contained any greater numbers of the organisms than did those of normal persons.

MacNeal, Latzer and Kerr,<sup>13</sup> Simonds,<sup>11</sup> Dudgeon,<sup>14</sup> Nye,<sup>15</sup> Moench, Kahn and Torrey,<sup>16</sup> Hines,<sup>17</sup> Davidson<sup>18</sup> and others found that *Cl. Welchii* may be present in considerable numbers in the feces of from 30 to 100 per cent of normal persons. In those studies in which quantitative determinations were made, the figures reported were lower

TABLE 1—*Summary of Results of Tests for Clostridium Welchii*

	Stormy Fermentation in Milk				Count per Gram in Ferrie Chloride and Sodium Sulphite Agar				
	Unheated Specimen		Specimen Heated at 80 C						
	Num ber Tested	Number Posi tive	Num ber Tested	Number Posi tive					
						Number with Counts of			
					Number Tested	1,000	1,000 to 100,000	100,000 to 10,000,000	10,000,000
Patients with severe car bohydrate intolerance	22	8	27	20	24	5	6	9	4
Patients with mild car bohydrate intolerance	13	8	23	19	20	3	4	9	4
Patients with hypo chromic anemia	3	3	3	3	3	0	1	2	0
Patients with gastro intestinal disturbances	4	1	6	4	7	1	2	3	1
Normal persons	10	9	14	12	14	3	5	6	0

than those obtained in our series. For example, Nye<sup>15</sup> gave 240 organisms per gram as the average count for six normal persons, and the highest counts reported by MacNeal, Latzer and Kerr,<sup>13</sup> Hines,<sup>17</sup> and Simonds<sup>11</sup> were 39,449, 6,000 and 15,600 per gram, respectively. However, only spores were counted in the methods used by these investigators.

The count for *Cl. Welchii* showed absolutely no correlation with the severity of the symptoms. In fact, many of the patients with the most distressing symptoms had less than 100 of these organisms per gram of feces. An analysis of specific signs and symptoms as listed

13 MacNeal, W. J., Latzer, L. L., and Kerr, J. E. *J. Infect. Dis.* **6**: 571, 1909.

14 Dudgeon, L. S. A Study of the Intestinal Flora Under Normal and Abnormal Conditions, *J. Hyg.* **25**: 119, 1926.

15 Nye, R. N. *J. Clin. Investigation* **4**: 71, 1927.

16 Moench, L. M., Kahn, M. C., and Torrey, J. C. Analysis of the Fecal Flora in Thirty-Three Cases of Pernicious Anemia. *J. Infect. Dis.* **37**: 161, 1925.

17 Hines, L. E. *J. Infect. Dis.* **32**: 280, 1923.

18 Davidson, L. S. P. *J. Path. & Bact.* **31**: 557, 1928.

in the previous paper<sup>1</sup> showed no agreement between any of them, either alone or in combination, and the number of the organisms found. A possible exception to this statement might be the fact that of twelve patients with mucus in the stool, six had counts greater than 1,000,000 per gram. However, equally high counts were obtained for eleven patients with no mucus present.

Herter,<sup>9</sup> Simonds,<sup>11</sup> Nye,<sup>15</sup> Moench, Kahn and Torrey,<sup>16</sup> Davidson<sup>18</sup> and others found that patients with pernicious anemia

TABLE 2—Data Showing Lack of Correlation Between Various Features of the Fecal Flora

	Aciduric Organisms			Proteolytic Organisms  Proteo- lysis* in Beef Heart Medium	Cl Welchii		
	Growth in Acetic Acid Broth		Count in Whey Agar, Number per Gm		Stormy Fermentation in Milk		Count in Ferrie Chloride and Sodium Sulphite Agar, No per Gm
	1 fifth Normal	Tenth Normal			Heated (80 C)	Unheated	
Cases of carbohy- drate intolerance							
1	—	+	10,000	++	+	+	110,000,000
2	+	+	1,000	+++	+	+	1,600,000
3	—	+	200	+	+	—	1,000,000
4	—	+	800	++	—	—	<100
5	—	+	1,200,000	+++	+	—	25,000,000
6	—	+	141,000	+	—	—	<100
7	—	—	3,000	++	+	—	40,000
8	—	—	1,600	++	—	—	15,000
9	—	—	16,000	+	+	—	150,000
10	+	+	200	+++	+	+	500
11	—	+	2,500,000	+++	+	—	3,000,000
12	—	+	1,200	++	+	—	13,100
13	+	+	170,000,000	+++	—	—	<100
14	—	—	<100	+++	+	+	164,000
15	+	+	<100	+++	—	—	300
16	—	—	41,000	++	—	—	1,000
Other gastro intes- tinal cases							
17	—	+	270,000	+++	—	—	<100
18	—	+	8,400	+++	—	—	<100
19	—	+	6,300	+++	+	—	30,000,000
20	—	—	13,400,000	++	+	—	1,700,000
21	+	+	3,200	+++	—	—	<100
22	—	—	700	+++	+	+	8,200,000
23	—	+	13,400,000	++	+	+	200,000

\* + indicates proteolysis in dilutions up to 1:1,000; ++, proteolysis in dilutions up to 1:100,000; +++, proteolysis in dilutions up to 1:1,000,000 or higher.

almost invariably show a great numerical increase of Cl. Welchii in the intestine. It is commonly believed that the increased number of these and other organisms in a patient in this condition is due, at least in part, to the achlorhydria and the consequent altered reaction of the contents of the small intestine. In view of this, it seemed reasonable to expect that the patients in this series who showed hypochlorhydria would also harbor large numbers of these organisms. However, of twenty-one patients with a low content of gastric hydrochloric acid only five showed counts exceeding 1,000,000 per gram, whereas six of thirteen with normal gastric acidity also gave high counts.

Cl Welchii was isolated from the feces of thirty-seven of forty-four patients unable to tolerate carbohydrate, of eight of ten patients with other disturbances and of twelve of fourteen normal persons. All the strains were strongly hemolytic, and they fermented starch both in the form of soluble starch and in potato mash. All four of Simonds' types were found, with types II and IV predominating. There was no relation between the type present and the clinical condition.

*Stormy Fermentation Tests*—It can be stated that the stormy fermentation test in milk was found to be of no diagnostic value as far as this condition was concerned. As can be seen in table 1, specimens from normal persons and from those suffering from other diseases showed as large a proportion of positive results from fermentation tests as did those from patients with symptoms of intolerance of carbohydrate. The number of positive reactions as well as the degree of fermentation was greater in the heated tubes than in the unheated ones where the growth of Cl Welchii often was inhibited, presumably by the presence of large numbers of other organisms. The quantity of inoculum was found to influence the results. When the inoculum for the unheated tubes was increased to 0.1 Gm., about 75 per cent of the specimens gave positive results regardless of their source, and with an inoculum of 0.5 Gm., every specimen tested, with the exception of one from a normal person, gave positive results.

Statements have been made by Hewes and Kendall,<sup>19</sup> Torrey<sup>20</sup> and others to the effect that stormy fermentation in milk inoculated with unheated fecal material indicates either a predominance of Cl Welchii, or at least an abnormal number of the organisms, in the intestinal flora or else unusually reduced numbers of acidogenic bacteria. Stormy fermentation is considered by many to indicate an abnormal intestinal flora. These statements were not borne out by the data given in table 2. It even has been stated that the amount of gas in the fermentation tube is a direct index of the relative number, or even the absolute number, of the organisms present. This is obviously a fallacy since an inoculum of even a few organisms can produce maximum fermentation if conditions chance to be such that multiplication occurs. This is such an elementary point that it may seem unnecessary to stress it, but failure to appreciate it seems to have caused much confusion.

A comparison of the fermentation tests of the heated specimens with the quantitative counts showed that there was no greater effect on milk whether the inoculum contained 5 of the organisms or 100,000,000 per gram. Although in the unheated tubes as few as 5 or 10 organisms

19 Hewes, H. F., and Kendall, A. I. The Gas Bacillus as an Agent of Intestinal Fermentation and Diarrhea, Boston M. & S. J. **166** 75, 1912.

20 Torrey, J. C. The Fecal Flora of Typhoid Fever and Its Reaction to Various Diets, J. Infect. Dis. **16** 72, 1915.

occasionally produced fermentation, in most instances at least 100,000 or more were necessary. On the other hand, it cannot be said that negative results from fermentation tests indicate the absence of the organisms or even a low count. Fifteen of the heated specimens failed to show growth although the counts were in several instances as high as 15,000,000 per gram, probably because the organisms were not in the spore state. Approximately 45 per cent of the unheated cultures failed to give fermentation, even though the counts ranged as high as 250,000,000.

*Presence of Aciduric Organisms*—Since it has been stated by Kendall<sup>21</sup> and others that aciduric organisms suppress the growth and activity of *Cl. Welchii* in the intestine, tests were made to determine how frequently and in what numbers these organisms were present in the feces. It was hoped that the results of such tests might serve to explain the discrepancies between plate counts and stormy fermentation tests. Tubes of acetic acid broth were inoculated as a qualitative and supposedly as a roughly quantitative test for aciduric bacteria. It was found that twentieth-normal acetic acid broth was of no value since growth of nonaciduric types occurred from every specimen tested. In fifth-normal and tenth-normal acetic acid broth the proportion showing growth was approximately equal for patients with carbohydrate intolerance and for normal persons, so that the test had no diagnostic significance.

Plate counts in whey agar varied from less than 100 to as high as 800,000,000 colonies per gram. Just as in the case of *Cl. Welchii*, there was no correlation between the qualitative tests in acetic acid broth and the quantitative plate count. Growth sometimes occurred in fifth-normal acetic acid broth when the whey agar count was less than 100, and growth at times failed to occur when the count was as high as 20,000,000. Organisms which developed in fifth-normal and tenth-normal acetic acid broth were members of the *Lactobacillus* group, streptococci and occasionally yeasts.

It can be seen in table 2 that there was no agreement between the ratio of aciduric organisms to *Cl. Welchii* and the occurrence of stormy fermentation in milk inoculated with unheated material. Apparently fermentation of milk by *Cl. Welchii* may occur in the test tube in the presence of large numbers of aciduric organisms, conversely, fermentation may fail, in some instances, even when the aciduric flora is numerically negligible.

*Presence of Proteolytic Organisms*—Aciduric bacteria are supposed to suppress the growth of proteolytic organisms, whereas *Cl. Welchii* has been said to accompany a predominantly proteolytic flora.<sup>21</sup> Accord-

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<sup>21</sup> Kendall, A. I. Further Studies on the Use of the Fermentation Tube in Intestinal Bacteriology, *J. Biol. Chem.* **6** 257, 1909.

ingly tests for protein-splitting organisms were made by culturing serial dilutions in beef heart medium as described

Proteolysis occurred over a wide range of dilutions with every stool tested regardless of the character of the aerobic flora and the source of the specimen. In ten samples the digestion of the meat occurred only up to a dilution of 1:1000. In all the rest there was evidence of proteolytic action of dilutions of from 1:10000 to 1:1000000 or occasionally even higher. As has been aptly pointed out by Sanborn -- no quantitative estimate of the degree of proteolytic activity of the anaerobic organisms in the feces is possible by such methods owing among other factors to differences in the absolute numbers and in the variety of the aerobes present. So far as the tests go, however, there was no correlation between proteolytic activity and any other factors studied viz. the symptoms or the count for Cl. Welchii or for aciduric organisms present.

Sanborn<sup>22</sup> also found that organisms capable of proteolytic action were often present in large numbers in feces in which many aciduric organisms could be demonstrated. Moreover specimens containing only a few organisms of the aciduric group gave no greater degree of proteolysis than did samples containing millions of organisms of this type. In children according to Morris, Porter and Meyer<sup>11</sup> the absence of aciduric organisms in strongly putrefactive stools is shown by sterile acetic acid broth tubes and marked growth in fifth-normal and tenth-normal acetic acid broth is indicative of a predominantly fermentative fecal flora. That this was not the case in the stools from adults included in this series is apparent in table 2 which shows clearly that proteolytic organisms may or may not reveal themselves in a highly diluted specimen which is capable of yielding growth in acetic acid broth.

*Fermentation of Potato Mash* — Since potatoes caused distress in this series of patients more commonly than other foods the fermentative action of the unheated fecal specimens on this starchy material was tested. No qualitative or quantitative differences were observed between the feces of those unable to tolerate carbohydrate and those of normal persons. Every specimen gave violent fermentation often blowing the plugs out of the tubes regardless of the amount of inoculum.

*Variations in Repeated Specimens from the Same Person* — When repeated specimens from the same person were studied there was considerable variation in the results particularly in the qualitative tests from day to day or from week to week. Although quantitative counts of Cl. Welchii might vary in repeated specimens even by as much as a hundredfold they were always consistently low or high as the case might be for the given person. On the other hand in qualitative tests

especially the stormy fermentation reaction, the results were extremely inconsistent. The fermentation might be present for two or three days and then suddenly disappear with little or no change in the count for *Cl. Welchii* or for aciduric organisms, in the diet or in the physical condition of the patient.

#### COMMENT

The bacteriologic studies of fecal specimens herein reported fail to reveal any etiologic relationship between *Cl. Welchii* and the syndrome described as intestinal intolerance of carbohydrate. There is no evidence that the feces of patients suffering from this disorder consistently contain any greater relative or absolute numbers of the organisms than do those of normal persons. Moreover, there is no reason to believe that a person harboring large numbers necessarily shows any manifestations of carbohydrate intolerance or similar gastro-intestinal disturbance. In the first place, the feces of a normal person may contain several millions of these organisms per gram. In the second place, in the cases of pernicious anemia reported by various authors<sup>23</sup> apparently the patients showed no signs of this condition, even though *Cl. Welchii* was present in the stools in enormous numbers. There seems to be no more reason to incriminate *Cl. Welchii* than any of the other gas-producing organisms constantly found in the intestine, although it is possible that this organism may be significant in individual cases, especially if it is multiplying in the ileum or jejunum.

The number of these organisms in the stool seems to have no relation to the number of aciduric or of proteolytic organisms found. The proportion of aciduric bacteria present apparently has no effect on the clinical condition of a person although the presence of these organisms is commonly considered to be beneficial.

It must be realized, of course, that these conclusions are based on studies of fecal specimens which in all probability do not fairly represent the intestinal flora. Simonds<sup>11</sup> stated the belief that the number of spores of *Cl. Welchii* found in the feces is a reliable index of the number of these organisms in the intestine provided that the specimens are examined within three hours after collection and that the fecal material has not remained in the colon for too long a time. However, the fecal flora probably differs greatly from that of the intestinal mucosa.

It is evident that various physiologic factors must be involved. These factors have been discussed in detail in the previous paper<sup>1</sup> and include the effect of diet, the upward extension of the colonic flora into the ileum and jejunum, the influence of lowered gastric acidity, the presence of increased amounts of carbohydrate in the colon and inter-

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23 Herter<sup>3</sup> Simonds<sup>11</sup> Nye<sup>15</sup> Moench, Kahm and Torrey<sup>16</sup> Davidson<sup>18</sup>

ference with the absorption of gas from the intestinal lumen. It is felt that the problem is as much a physiologic as a purely bacteriologic one.

Obviously, the bacteriologic possibilities have not been exhausted, and further investigation may reveal an etiologic relationship between the bacterial flora and this intestinal disturbance. Studies of the bacterial content of the small intestine would be of special value. The possible antagonistic action of *Bacterium coli* or other organisms on certain bacteria in the intestine should be considered. It may be significant that mucus was found in the stools of all patients who were not benefited by treatment,<sup>1</sup> and the relation of *Clostridium Welchii* and of other bacteria to the presence of mucus should be studied.

In the present state of our knowledge the clinical laboratory can be of little or no assistance in the diagnosis of this and similar intestinal disturbances. The tests carried out as a routine seem to be more misleading than helpful. This is particularly true of the stormy fermentation tests. Since the stools of nine of ten normal persons give positive results for fermentation, it can be of no diagnostic value. Even Hewes and Kendall,<sup>19</sup> who advocated such tests, admit that *Cl. Welchii* may be present in normal feces in sufficient numbers to give stormy fermentation. Moreover, the variation in results with repeated daily specimens from the same person would in itself render the test valueless.

No existent method of bacteriologic examination of the feces, no matter how elaborate and painstaking it may be, can give an accurate estimate of the extent and character of the activity of the bacteria within the intestinal tract. Hence, for the present, the diagnosis of intolerance of carbohydrate must be based entirely on clinical observations. If a particular dietary regimen affords relief to a given patient, it should be followed, regardless of whether it alters the intestinal flora as judged by reactions in the test tube.

#### SUMMARY AND CONCLUSIONS

Fecal specimens from persons suffering from a clinical syndrome designated as intolerance of carbohydrate were studied bacteriologically by both qualitative and quantitative methods.

The incidence of *Cl. Welchii* ranged from a minimum extreme of less than 100 to a maximum extreme of 250,000,000 organisms per gram. "Stormy fermentation" tests in milk were positive with the majority of specimens, without regard to the number of the organisms present. Plate counts for aciduric organisms varied from less than 100 to 800,000,000 per gram. Dilutions of specimens as high as 1:1,000 to 1:1,000,000 resulted in proteolysis when incubated in beef heart broth. Potato mash, a food causing much distress in patients, was violently fermented by all specimens in test tube cultures. Repeated



specimens from a given person often indicated a variation in flora under constant conditions nearly as great as that obtained in different persons

These results were equally true for specimens from normal persons tested as controls

Correlations of these results with each other indicate that 1 The "stormy fermentation" test is not a reliable index of the presence of *Cl. Welchii* or of any other predominant types of organism 2 The presence of aciduric organisms does not necessarily influence the "stormy fermentation" test, nor does their presence afford any clue as to the incidence of *Cl. Welchii* 3 Proteolytic organisms occur in high frequency and in considerable numbers, without regard to the presence of aciduric types or of *Cl. Welchii* 4 Violent fermentation of potato mash occurs in most specimens, without regard to evidence of intestinal symptoms

No evidence was obtained by the fecal culture methods used in these experiments that *Cl. Welchii* bears any direct etiologic relationship to the clinical condition under observation There was distinct evidence that certain tests which have been suggested for laboratory diagnosis, as well as more elaborate special tests, definitely fail to aid in diagnosis and merely cause confusion

# RENAL LESIONS IN STAPHYLOCOCCUS AUREUS INFECTIONS AND THEIR RELATION TO ACUTE GLOMERULAR NEPHRITIS

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DURHAM, N C

Dyke<sup>1</sup> adequately studied the method of elimination of Staphylococcus through the kidneys and also the pathogenesis of the lesions produced by this organism. It was his opinion that the passage of organisms "from the blood stream to the urine occurs only as the result of the formation of lesions in the kidney substance. The steps leading to the formation of such lesions after the introduction of cocci into the blood stream appear to be something as follows. The first cocci to find their way to the kidneys are held up in the glomeruli and there destroyed. Later, coccic emboli lodge in the vessels afferent to the glomeruli, these multiply and give rise to abscesses in the cortex and boundary zone. Even before a definite abscess is established, organisms find their way through the damaged vessel walls and tubular epithelium and gain ingress to the lumina of the tubules."

Recently Rigdon, Joyner and Ricketts<sup>2</sup> described the lesions in the kidneys of rabbits following the intravenous injection of an exotoxin from a hemolytic strain of Staph aureus. It was their opinion that the toxin injures the epithelial and endothelial cells of the glomerular tufts and the epithelial cells of the convoluted tubules and the loops of Henle. Any degree of injury may be found, from simple cloudy swelling to complete cellular disintegration. In the early stage the capillary loops of the tufts are dilated and filled with red blood cells, whereas later the capillaries contain few red blood cells. In the early process the endothelial cells of the tufts are swollen and a few are destroyed. Some of the glomeruli are severely injured by the toxin, as shown by the presence of desquamated cells, leukocytes and red blood cells in the capsular space, by the presence of adhesions between the tuft and the capsule and by thrombi in the capillary loops.

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From the Department of Pathology, Duke University School of Medicine

1 Dyke, S C. On the Passage of the Staphylococcus Aureus Through the Kidney of Rabbits, J Path & Bact **26** 164 (April) 1923

2 Rigdon, R H, Joyner, A L and Ricketts, E T. A Study of the Action of a Filtrable Staphylococcus Toxin on the Kidney of Normal Rabbits, Am J Path **10** 425 (May) 1934

From these studies it is evident that the lesions produced in the kidney by *Staph aureus* are different from those produced by an exotoxin from a hemolytic strain of *Staph aureus*

Seven patients with infection with *Staph aureus* were studied to determine if there were lesions in the kidneys which correspond to those produced by bacteria and an exotoxin and if there was clinical evidence of glomerular nephritis when both types of lesions were present

#### REPORT OF CASES

CASE 1—L. R., a 28 year old white woman, was admitted to the Duke Hospital on March 1, 1933, with headache and fever. Two weeks before she had a cold and a slight hacking cough. One week previous to admission her neck "became sore," and this was accompanied by enlargement and tenderness of the lymph nodes in the cervical group on the right side.

The patient as a child was never healthy. She had measles, mumps, whooping cough and typhoid. There was no history of diphtheria, scarlet fever, pneumonia, pleurisy, rheumatic fever, or chorea. In 1918, after an attack of influenza her feet were swollen and so painful that she was unable to walk, unfortunately there was no additional information with regard to the extent and duration of this edema. In 1919 tonsillectomy was performed, and in 1924 an operation for intestinal obstruction. Several years previous to admission a rectal abscess was drained. Three years before she had unilateral otitis media.

On examination the temperature was 38.2 C (101 F), the pulse rate 96 per minute, the respiratory rate 20 per minute and the blood pressure 115 systolic and 95 diastolic. The posterior portion of the pharynx was slightly hyperemic. The lymph nodes at the angles of the jaws were enlarged but tender only on the right. A few colonies of beta hemolytic streptococci were present in a culture of material from the throat. The white blood cell count was 9,400, and the red blood cell count was 3,500,000. The urine contained a slight trace of albumin and a few pus cells. Four days later there was an increase in the quantity of albumin in the urine and in addition red and white blood cells were present. The temperature returned to normal approximately forty-eight hours after admission. The soreness in the throat diminished, and the patient was discharged four days later.

Four days after discharge she was readmitted, with the temperature 37.8 C (100.8 F), the pulse rate 80 per minute, the respiratory rate 20 per minute and the blood pressure 115 systolic and 78 diastolic. A culture of material from the throat showed many colonies of alpha hemolytic streptococci and a few colonies of beta hemolytic streptococci. A large, firm red area below the angle of the mandible on the right proved to be an abscess, this was drained and the cultures showed *Staph aureus*. Approximately ten days after the operation there developed edema of the face and lower extremities, nausea and general malaise. The nonprotein nitrogen content of the blood was 43 mg per hundred cubic centimeters, and the urine showed albumin, red and white blood cells and cellular and granular casts. The blood pressure was 160 systolic and 104 diastolic.

While in the hospital the patient acquired pain in the flanks and in the suprapubic region with burning pain on urination. Through the cystoscope the wall of the bladder was seen to be inflamed, and bloody urine spurted from both ureteral orifices. *Bacillus coli* was obtained in pure culture from the right kidney. A test for renal function on May 10, approximately two months after the abscess in the neck was drained, showed 18 per cent phenolsulphonphthalein excreted in the

first half hour and 8 per cent during the second half hour. The urine contained blood over a period of two months. On May 11 the blood pressure was 170 systolic and 108 diastolic, and a modified Mosenthal test gave the following results

Time	Specific Gravity
8 a m	1 010
10 a m	1 015
12 noon	1 017
2 p m	1 017
4 p m	1 022
6 p m	Quantity insufficient

On May 12 the nonprotein nitrogen content of the blood was 40 mg per hundred cubic centimeters, the refractive index 1.351 and the total protein 6.1 Gm per hundred cubic centimeters.

The patient was last seen about two months after the onset of the illness. No information could be obtained as to her health one year later.

CASE 2—C. B. J., a 43 year old white man, was admitted to the Duke Hospital on May 30, 1932, complaining of "pain and throbbing" in the right hip for six weeks.

At the age of 14 the patient fell and injured that hip. He remained in bed for several months, at which time the hip was incised and drained. A total of seventeen operations had been performed on the hip, the majority being for drainage.

On examination the temperature was 37 C (98.6 F), the pulse rate 80 per minute, the respiratory rate 18 per minute and the blood pressure 130 systolic and 90 diastolic. The right leg was 4 inches (10 cm) shorter than the left, and the femur was rigidly fixed to the pelvis in such a position as to produce marked flexion of the thigh. There was considerable pain when the right thigh was moved. A roentgen examination showed destruction of the bone about the head of the femur and acetabulum.

On June 7 the right hip was drained, a culture of the pus showed *Staph aureus*. The day after operation the temperature rose from 38.3 to 40 C (from 101.2 to 104 F), and it continued to be elevated until the end. On June 23 a blood culture showed *Staph aureus*. The patient grew progressively worse and died on June 29.

A specimen of the urine examined on May 30 contained a trace of albumin, an occasional white blood cell and from 1 to 3 epithelial cells per high power field. Another specimen, examined on June 23, contained no albumin and only an occasional white blood cell.

*Autopsy*—(Only the essential observations are recorded in all of the autopsy reports.) The right leg was from 6 to 8 cm shorter and much smaller than the left, the latter was partially fixed in abduction. There were several scars and a recent incision in the area of the right hip. When this region was explored several sinuses and pus pockets were found and a large amount of scar tissue. The head of the right femur and the right ilium showed the characteristic lesion of chronic osteomyelitis with an acute exacerbation.

There were fibrinous adhesions between the layers of pleura on both sides of the thoracic cavity and a localized empyema on the anterior surface of the left lung. Many small abscesses were present throughout both lungs, some extend-

ing through the visceral layer of pleura. Groups of gram-positive cocci were present in the abscesses.

The heart weighed 330 Gm. Many small abscesses were found in the myocardium. The spleen weighed 340 Gm and was an acute splenic tumor. The liver weighed 2,400 Gm and was normal.

Both kidneys were essentially the same size. Small abscesses and a few cysts were found when the capsule was removed. There were small scars in the cortex of the kidney, mononuclear cells and a few polymorphonuclear leukocytes were present in these areas. Hyaline glomeruli were found in the scars, and usually the adjacent renal tubules were atrophic or had completely disappeared. In some glomeruli the capillary loops were filled with hyaline material, and often adhesions were present between these loops and the capsule. Sometimes Bowman's capsule was greatly thickened, resembling a hyaline membrane. Red blood cells were found in the lumens of the tubules adjacent to some of the glomeruli with adhesions. There was no evidence of inflammation in those glomerular tufts which were surrounded by red blood cells. The lumens of the tubules often contained hyaline casts in addition to red blood cells.

Cultures of the blood from the heart and of material from the sinuses in the right hip and from the pleural cavity showed *Staph aureus*.

CASE 3—A. B., a 6 year old white girl, was admitted to the Duke Hospital on June 16, 1932, with a swollen left knee. The swelling was first observed three months before by a salesman when the patient was buying a pair of shoes. The knee continued to swell and became painful only one week before admission.

On examination the temperature was 40.2 C (104.6 F), the pulse rate 160 per minute and the respiratory rate 44 per minute. The left leg was swollen, especially about the knee and ankle. The skin over the entire extremity was red and tender. A blood culture showed *Staph aureus*. The leg was incised and drained. The white blood cell count varied from 18,000 to 60,000 per cubic millimeter. The urine was normal. A septic type of temperature persisted, and death occurred four days after admission.

*Autopsy*—There were two incisions approximately 6 cm in length on the anterior surface of the left leg. The muscles in this leg were edematous and hemorrhagic, those on the lateral side of the upper third of the tibia were separated from the bone by pus. Many fibrinous adhesions were present between the layers of pleura on both sides of the thoracic cavity, and numerous abscesses were found in the viscera.

The abscesses were very diffuse in the kidneys, some apparently had their origin in the glomerular tufts. Hyaline thrombi were present in approximately 10 per cent of the glomeruli. A detailed study of the thrombi with Heidenhain's hematoxylin stain showed that they varied in size and shape and often occluded the capillary loops. The endothelial cells lining the capillaries around the thrombi could not be easily demonstrated (fig 1). The thrombi did not show fat when stained with scarlet red, nor could fibrin and bacteria be demonstrated in them with the Goodpasture-MacCallum bacterial stain. Red blood cells in the lumens of the tubules were conspicuous in the kidney.

CASE 4—A. H. Z., a 40 year old white woman, was admitted to the Duke Hospital on Dec 26, 1933, for a thoracoplasty for pulmonary tuberculosis. In 1928 or 1929 the patient noticed "pus in strings" in the urine on numerous occasions, this was accompanied by a high fever. There was no history of dysuria, hematuria or the passage of stones.

The urine was examined approximately once a month for the three years preceding admission to this hospital. In the voided specimens a small amount of albumin was often found and white and red blood cells. Granular casts were reported three times in the thirty-one specimens examined, however, in a catheterized specimen examined on Sept 9, 1932 there was no albumin, casts or red blood cells, and only a few white blood cells and epithelial cells were seen.

On admission the temperature was 37 C (98.6 F), the pulse rate 80 per minute, the respiratory rate 18 per minute and the blood pressure 110 systolic and 66 diastolic. A roentgen examination of the chest showed an old fibrous tuberculous process in the right apex, and the entire left lung was obscured,

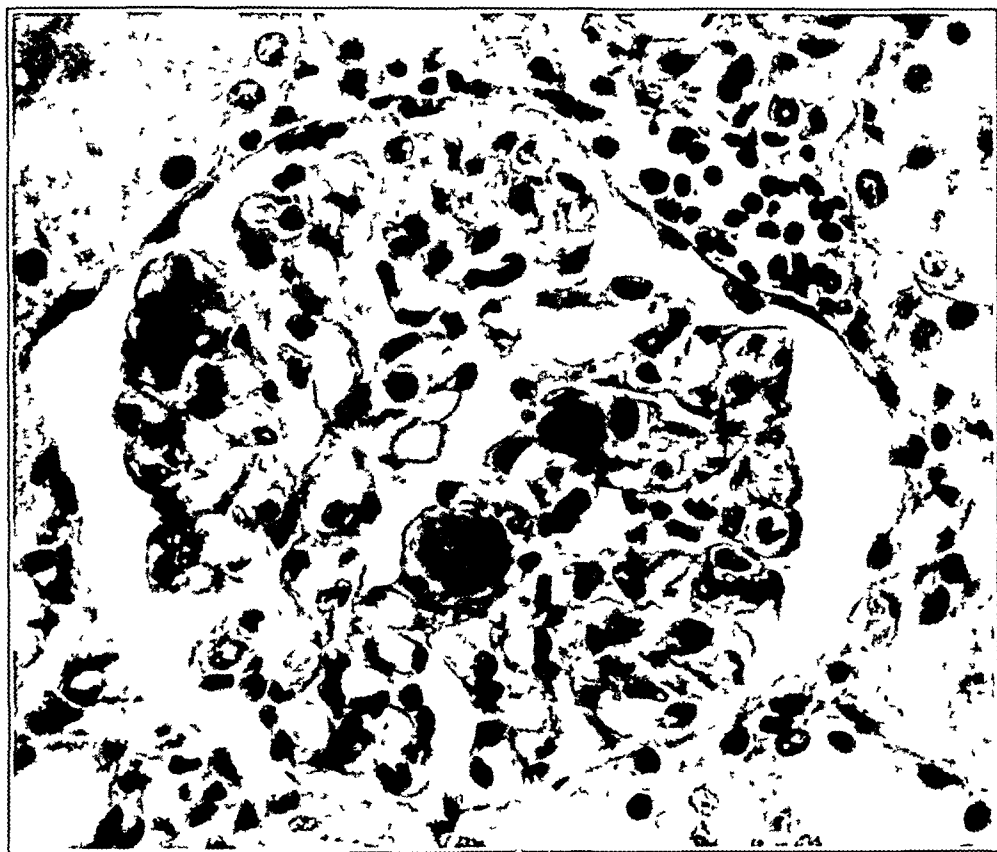


Fig 1 (case 3)—Photomicrograph showing thrombi in the glomerulus, which seem to be formed from the necrotic and coagulated endothelial cells of the capillary loops. This lesion occurred in a child 6 years old who had acute osteomyelitis of the tibia and *Staph aureus* septicemia.

probably by a thickened pleura and a tuberculous infiltration of the parenchyma. The heart and mediastinum were displaced to the left, the left side of the diaphragm was elevated to the seventh interspace, posteriorly. The white blood cell count was 10,440. The urine was normal.

The first stage of an extrapleural thoracoplasty was performed on Jan 3, 1932. Two days after operation a culture of the wound showed *Staph aureus*. The temperature reached 39 C (102.2 F) on the sixth postoperative day, however, it returned to normal on the fourteenth postoperative day.

Table 1 gives the specific gravity and an estimated amount of albumin in the urine during the time the patient was in the Duke Hospital. Table 2 gives the results of quantitative determinations of the albumin content (Esbach method).

from March 10 to March 16, 1934 Table 3 shows the result of Volhard concentration and water dilution tests<sup>3</sup> made on April 20, three and one-half months after the onset of the Staph aureus infection in the thoracic wall

TABLE 1—*Specific Gravity and the Estimated Amount of Albumin in the Urine During the Time the Patient Was in the Duke Hospital*

Date	Specific Gravity	Estimated Amount of Albumin
12/30/33	1 007	0
1/ 3/34	1 013	0
1/ 4/34	1 030	0
1/10/34	1 026	1 plus
1/12/34	1 013	2 plus
1/13/34	1 023	4 plus
1/22/34	1 013	3 plus
1/31/34	1 015	3 plus
2/ 7/34	1 015	3 plus
2/21/34	1 026	3 plus
2/27/34		2 plus
3/ 7/34	1 021	2 plus
3/17/34	1 022	2 plus
3/21/34	1 018	1 plus
3/28/34	1 012	trace
4/18/34	1 020	1 plus
5/ 2/34	1 023	trace
5/ 9/34	1 010	trace

TABLE 2—*Results of Quantitative Determinations of Albumin in the Urine (Esbach's Method)*

Date, 1934	Total Amount of Urine Excreted in Twenty Four Hours, Cc	Gm of Albumin Excreted in Twenty Four Hours
3/10	1,245	1 50
3/11	570	1 14
3/12	1,660	2 15
3/13	1,685	2 86
3/14	1,395	2 50
3/15	1,580	2 60
3/16	2,140	3 40

TABLE 3—*Results of Volhard Concentration and Water Dilution Tests*

Time	Patients		Controls	
	Amount of Urine, Cc	Specific Gravity	Amount of Urine, Cc	Specific Gravity
8 00 a m			42	1 018
8 30 a m	35	1 007	250	1 001
9 00 a m	35	1 008	360	1 000
9 30 a m	175	1 001	310	1 000
10 00 a m	175	1 001	135	1 002
10 30 a m	205	1 000		
11 00 a m	255	1 001	65	1 010
11 30 a m	175	1 001	35	1 020
12 00 noon	250	1 001	20	1 020
2 00 p m	205	1 004	80	1 020
4 00 p m	50	1 012	70	1 022
6 00 p m	60	1 015	100	1 022
8 00 p m	35	1 028	105	1 026

3 The procedure is given in a book by Elywin (Nephritis, New York, The Macmillan Company, 1929, p 33)

On May 1 the nonprotein nitrogen content of the blood was 30 mg, the urea nitrogen content 11.5 mg and the chloride content of the plasma 484 mg per hundred cubic centimeters. The carbon dioxide capacity was 57 volumes per cent and the refractive index 1.349, the urea clearance was 62 per cent for the first specimen and 44 per cent for the second. The patient was discharged on May 12, approximately five and one-half months after admission, with only a trace of albumin in the urine and a normal nonprotein nitrogen content of the blood.

CASE 5—W. S., a 13 year old Negro boy, was admitted to the Duke Hospital on Nov. 6, 1933, with pain and swelling of the left ankle, forearm and wrist. Six days before admission, while standing on a chain that was suddenly jerked, he injured the left ankle. The following day there was some pain about the ankle, but he continued to walk. Two days after the accident the pain and swelling was so severe that he had to remain in bed. During this time the rate of the respirations increased, and pain developed in his chest. The pain and swelling in the forearm and wrist developed only two days before admission.

On examination the temperature was 40.5 C (105.4 F), the pulse rate 160 per minute, the respiratory rate 60 per minute and the blood pressure 110 systolic and 90 diastolic. There was no abrasion in the skin of the leg. A friction rub was heard on both sides of the chest and also in the precordial region. The left leg was edematous and warm. There was some tenderness about the left wrist. A culture of the blood showed *Staph. aureus*. The urine was normal. The patient died approximately ten hours after admission.

*Autopsy*—The left leg was greatly swollen from the knee down. There was no abrasion or bruise in the skin. The subcutaneous tissues were edematous. The tissues were hemorrhagic and necrotic in the area of the interosseous septum in the lower half of the leg. The periosteum was separated from the shaft of the tibia by a large amount of pus, some of which had infiltrated into the adjacent tissues. The bone marrow in the lower third of the tibia was necrotic.

There was fresh pericarditis, the cultures showed hemolytic staphylococci (*Staph. aureus*). The heart weighed 190 Gm and showed only a few small hemorrhages in the mitral valve. Both lungs were covered with a fibrinous exudate, and in section they showed many small abscesses. The liver weighed 1,130 Gm. Two small abscesses were found when the organ was sectioned.

The kidneys were swollen, and an abscess from 5 to 6 mm in diameter was present in the cortex of the left kidney. The tubular epithelium was often swollen and necrotic, and many of the cells contained hyaline droplets. Fat was demonstrated in the tubular epithelial cells with the scarlet red stain. Red blood cells were present in the lumens of many tubules. Thrombi similar to those in case 3 were found in the afferent arterioles and in the capillaries of the glomerular tufts.

The mucosa of the colon was poorly preserved. In it were areas of necrosis and hemorrhage, and portions were covered with a diphtheritic membrane. Thrombi were present in the capillaries in the mucosa which resembled those in the capillaries of the kidney.

CASE 6—W. R., a 26 year old white man, was admitted to the Duke Hospital on Nov. 8, 1933, with a history of a severe occipital headache for thirteen days. The patient was hit on the head with a shovel approximately two months before the onset of this headache. He was unconscious for several hours after the injury and had a headache for a few days. A dull pain in both hips and a non-productive cough began several days before admission.



In 1922 the patient had gonorrheal urethritis which was followed by arthritis

At the time of admission the temperature was 41 C (105.8 F), the pulse rate 100 per minute, the respiratory rate 24 per minute and the blood pressure 98 systolic and 64 diastolic. The heart was slightly enlarged in all diameters. A systolic murmur was heard over the precordium, this was loudest at the apex. The lungs were normal. There was slight tenderness in both lower quadrants.

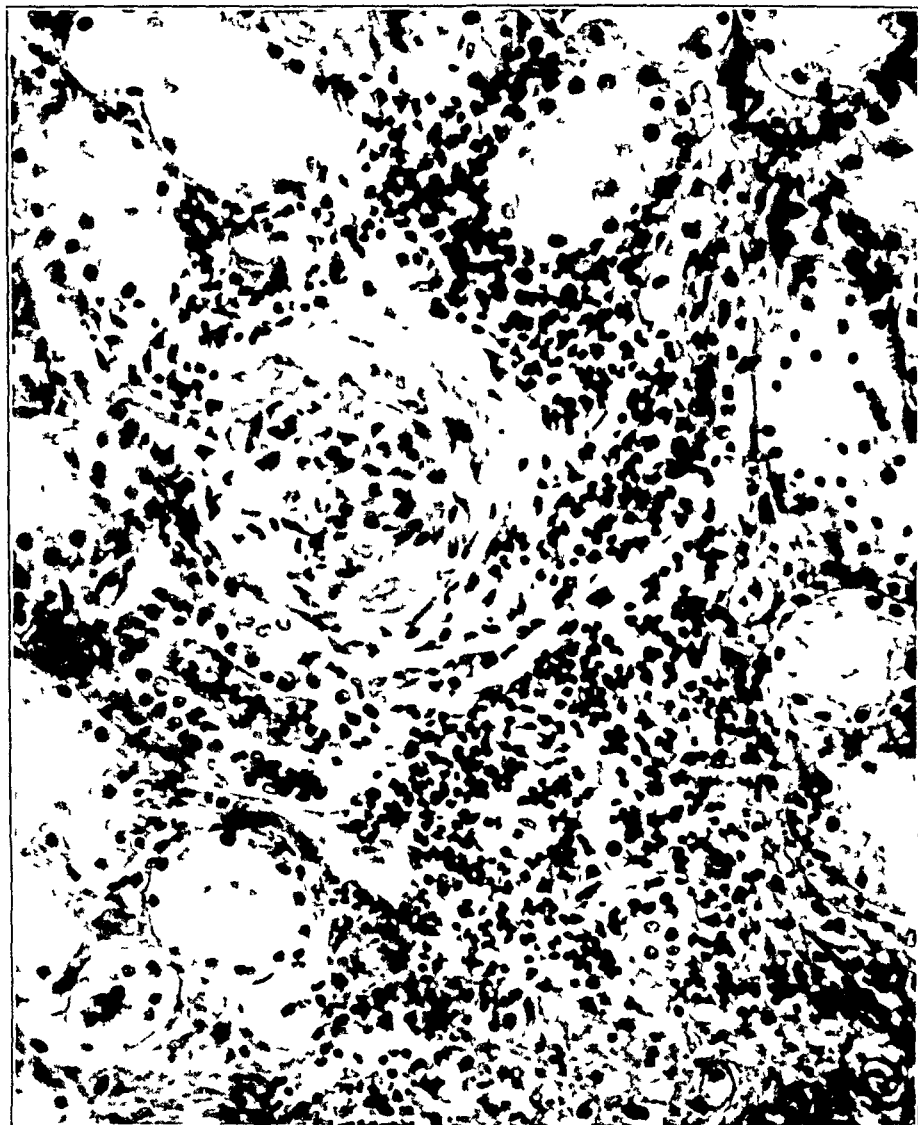


Fig 2 (case 6) —Partial hyaline degeneration of a glomerulus with atrophy of the adjacent renal tubules and an infiltration of mononuclear cells into the area. The kidney in this case was taken from a man who had osteomyelitis of the skull, an abscess of the brain and *Staph aureus* septicemia. The skull was injured approximately two and one-half months before death.

and over the sacro-iliac region on the right. The thighs were flexed and when moved caused considerable pain.

There was a small area of tenderness in the left temporal region, and a roentgen examination showed what was thought to be acute osteomyelitis of the tem-

poral bone. A culture of the blood showed *Staph aureus* on the day of admission. The urine contained albumin (1 plus) and a few granular and hyaline casts. On Nov 9, 1933, the day after admission, an abscess in the scalp was opened, a portion of the infected skull removed and an extradural abscess drained. An abscess in the right buttock was incised, and an area of infection found about the head of the right femur was drained. Cultures of material from all areas showed *Staph aureus*. Twelve days after the first operation a second extradural abscess and an abscess in the temporal lobe of the brain were drained.

On November 15 the urine contained albumin (3 plus), red blood cells and white blood cells. Three days later the urine contained albumin (1 plus) and

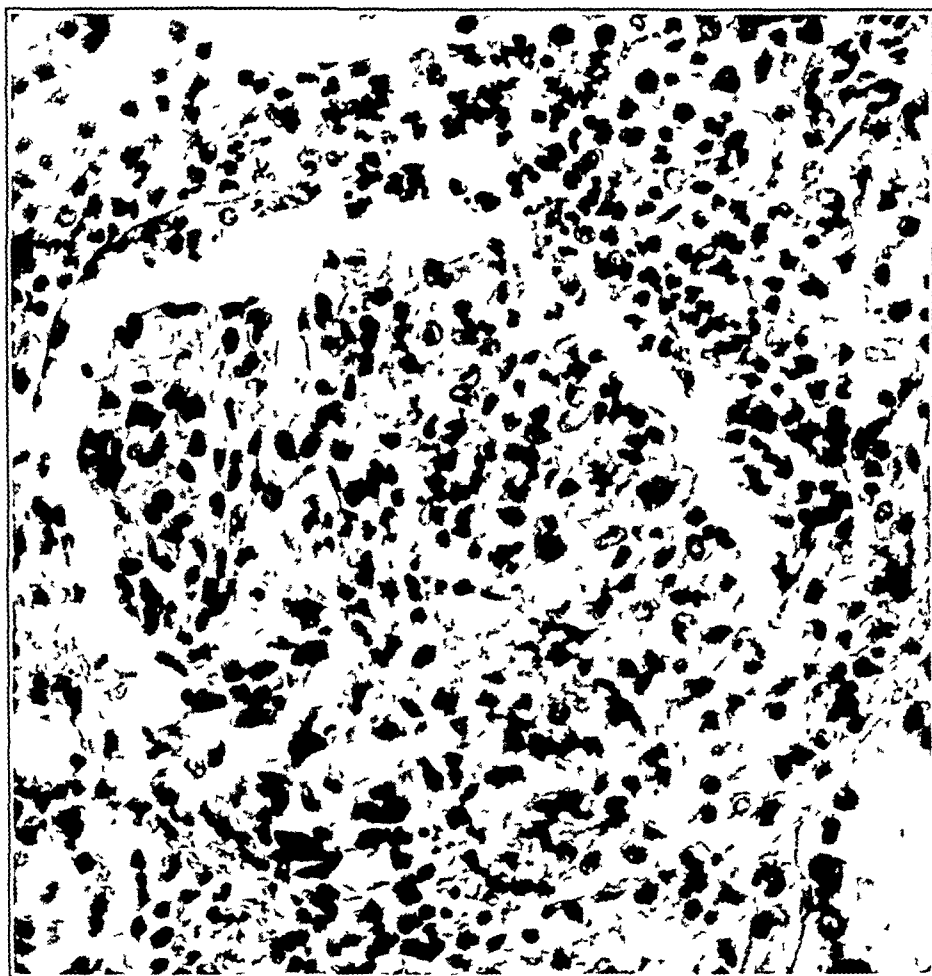


Fig 3 (case 6)—Acute glomerulitis in a case of osteomyelitis of the skull and *Staph aureus* septicemia

10 red blood cells and innumerable white blood cells per high power field. The patient grew progressively weaker and died on November 28, twenty days after entrance.

*Autopsy*—Pus could be expressed from the two incisions in the left temporal region of the scalp. There was a bony defect in the skull in this location and the adjacent bone showed extensive necrosis. The meninges were covered with a purulent exudate. The longitudinal sinus was occluded by a thrombus and the entering veins were dilated. Several abscesses and areas of hemorrhage were present in the cortex of the brain.

The two incisions in the skin over the right hip were infected. The head of the femur showed acute osteomyelitis. The pleura of both lungs was covered with a fibrinous exudate, and 250 cc of thin, cloudy fluid was present in the right thoracic cavity. Abscesses were found in both lungs. The heart weighed 350 Gm, and small abscesses were present in the myocardium. There was a small friable vegetation on the mitral valve. The spleen weighed 400 Gm and contained two large infected infarcts. The liver weighed 2,200 Gm. The thyroid gland was essentially replaced by small abscesses. There were several small superficial ulcers in the mucosa of the cecum and ascending colon, some measuring 1 cm in



Fig 4 (case 6) —Fibrous adhesions between the glomerular tuft and Bowman's capsule, red blood cells in the lumens of the tubules and degeneration of the renal epithelial cells in a case of osteomyelitis of the skull and *Staph aureus* septicemia

diameter. The kidneys were the same size and contained many abscesses and pinpoint hemorrhages. Numerous areas were seen in which groups of mononuclear wandering cells surrounded hyalinized glomeruli and extended down into the interstitial tissue (fig 2). Polymorphonuclear leukocytes had infiltrated into the tuft and the capsular space and had invaded the stroma surrounding Bowman's capsule (fig 3).

A hyalin-like thrombus occasionally occluded a capillary loop, and a few glomeruli had fibrous adhesions between the tuft and the capsule (fig 4). The most conspicuous feature was the presence of red blood cells in the capsular

spaces and in the lumens of the tubules (fig 5) One of the glomeruli was sectioned in such a way that the red blood cells could be seen extending from the capsular space into the neck of the renal tubules In some instances the lumens of the tubules around these glomeruli were filled with blood casts There were no demonstrable lesions in the majority of the tufts that were surrounded by red blood cells In some areas the endothelial cells were necrotic in those capillary loops which contained the pink-staining material The lesions in the glomeruli had no direct relation to the abscesses in other parts of the kidney

Red blood cells, hyaline casts, desquamated epithelial cells and calcified casts could be found in the lumens of some of the tubules The epithelial cells lining the tubules were often poorly preserved and sometimes contained fat

CASE 7—M C, a 71 year old white woman, was admitted to the Duke Hospital on Jan 15, 1934, for a mastectomy on the left side for carcinoma There

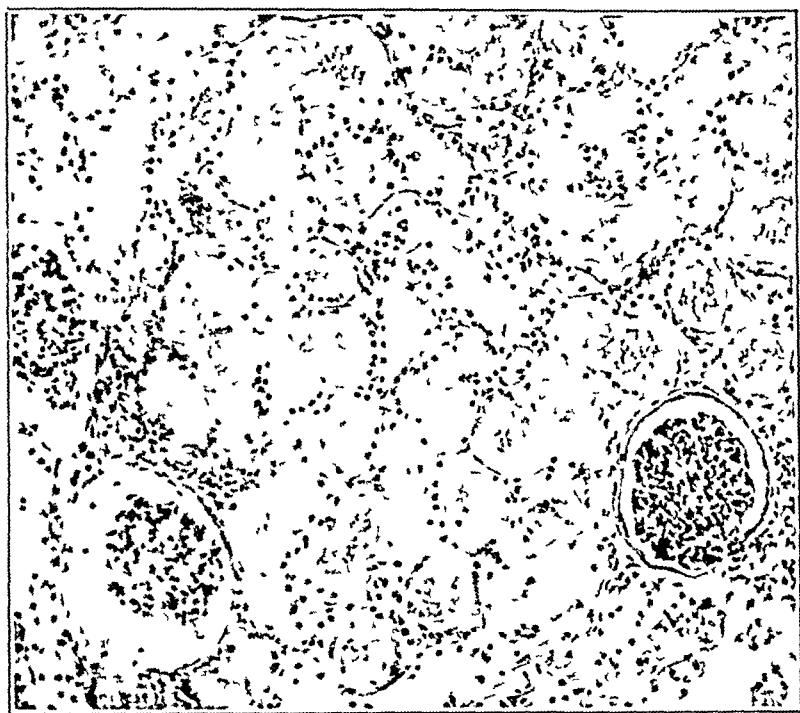


Fig 5 (case 6) —Red blood cells are present in the capsular space of one of the glomeruli and in the lumens of the tubules In one glomerulus the red blood cells in the capsular space are continuous with the cells in the neck of the renal tubule This lesion was found in a case of osteomyelitis of the skull with *Staph aureus* septicemia

was nothing important in the past history except the removal of the right breast for a benign tumor ten years previously The patient knew that she had had an elevated blood pressure for the past three or four years, but she had had no symptoms

On examination the temperature was 37 C (98.6 F), the pulse rate 84 per minute, the respiratory rate 28 per minute and the blood pressure 196 systolic and 105 diastolic The left nipple was retracted, and a firm irregular mass was palpable in the breast On January 15 the day preceding operation, a voided specimen of urine had a specific gravity of 1.01, it was acid in reaction and showed neither sugar nor albumin, an occasional white blood cell was present, but no red blood cells or casts were noted

At operation the left breast was removed and the axillary lymph nodes were resected. On the fourth postoperative day the patient had a chill, and the temperature reached 40.4 C (105.1 F). At this time a culture of material from the operative wound showed hemolytic staphylococci (*Staph aureus*), a culture of the blood gave negative results, and a catheterized specimen of urine was normal.

On the eighth postoperative day the temperature was still elevated, and the wound was explored and drained. A culture of the blood gave negative results at this time, and a catheterized specimen of urine showed albumin (1 plus) with from 15 to 20 white blood cells and an occasional hyaline cast.

On January 23 the nonprotein nitrogen content of the blood was 90 mg per hundred cubic centimeters, the chloride content (plasma) 498 mg, the uric acid content 7.7 mg, and the creatinine content 4.4 mg, the carbon dioxide capacity was 49.8 volumes per cent. A catheterized specimen of urine showed albumin (2 plus), some red and white blood cells and blood casts. A culture of the blood showed hemolytic staphylococci (*Staph aureus*) on January 26, the following day a voided specimen of urine contained albumin (1 plus), with approximately 16 white blood cells per high power field. The patient grew progressively worse and died on January 28, the fourteenth postoperative day. Autopsy was not performed.

#### COMMENT

The clinical picture in case 1 was characteristic of acute glomerular nephritis and resembled that in the cases with an associated streptococcal infection. A few streptococci were found in a culture of material from the throat of this patient but no more than it is usual to find in routine cultures made of material from the throat. The predominating infection was in the nodes on the right side of the neck, *Staph aureus* was cultured from the abscess. Cystoscopic examination made approximately two months after the abscess in the neck was drained revealed bloody urine spouting from the orifices of both ureters. An elevation of the blood pressure and the edema of the face and lower extremities showed definitely diminished renal function. In two months the blood pressure rose from 115 systolic and 95 diastolic to 170 systolic and 108 diastolic. Over a similar period the red blood cell count dropped from 3,500,000 to 2,540,000. There was a decrease from the normal in the specific gravity with a tendency toward fixation, as shown by the Mosenthal test.

The urinary findings in case 4 supplied the only data on which a diagnosis of acute nephritis could be made. The reaction for albumin was 1 and 2 plus on the seventh and ninth postoperative days, respectively, and 4 plus on the tenth postoperative day. Albumin persisted in considerable amounts (3 and 4 plus) for approximately five weeks, afterward the amount gradually decreased. There was only a trace of albumin in the urine when the patient was discharged five months after operation.

There was an increase in the amount of albumin in the urine as estimated quantitatively (table 2). It is interesting to note that these

examinations were made when there was a decrease in the estimated amount of albumin. The data obtained from the water dilution and concentration tests indicate renal insufficiency.

Although the patient in case 7 had an elevated blood pressure before operation, there were no symptoms of renal insufficiency and the urine was normal. On the ninth postoperative day a catheterized specimen of urine showed albumin (2 plus), red blood cells and blood casts, the nonprotein nitrogen of the blood was 90 mg per hundred cubic centimeters. It is plain that the kidney had sustained damage following an infection with a hemolytic strain of *Staph aureus*.

There was nothing in the history, physical examination or laboratory findings in cases 2, 3 and 5 to suggest any renal damage. In case 6 the urine showed albumin, red blood cells and hyaline and granular casts.

The lesions in the kidneys help to interpret the clinical observation made in cases 1, 4, 6 and 7. The kidneys in all these instances had red blood cells in the lumens of the tubules. Sometimes only a few groups of tubules were involved, and in other cases the process was very diffuse. The red blood cells in the lumens of the tubules in one case were shown to have their origin from the blood in the glomerular space.

Sometimes the epithelial cells in the convoluted portion of the renal tubules were swollen and contained hyaline droplets. The lumen was dilated in this portion of the tubules, the epithelial cells were cuboidal, resembling those that MacNider<sup>4</sup> described as regenerated cells. Albumin, hyaline casts and red blood cells were seen in the lumens of the tubules in all the kidneys studied pathologically.

The thrombi found in capillary loops of some of the glomeruli were not "hyaline thrombi." They were apparently formed by fusion of endothelial cells which had undergone necrosis. Those thrombi did not contain either fibrin or fat, bacteria could not be demonstrated in them. Baehr<sup>5</sup> described similar thrombi in the kidney in the early stages of glomerular nephritis and stated that hyaline thrombi represented the healed stage of the type of thrombi found in the capillaries in these cases.

Some of the glomeruli which had thrombi in the capillaries had adhesions between the loops and Bowman's capsule. Fibrous adhesions were present between some of the tufts and Bowman's capsule in which there were no capillary thrombi. Some of the glomeruli were represented by a mass of hyaline tissue, the tubules about these glomeruli were collapsed, and the adjacent tissue was infiltrated with mononuclear cells.

4 MacNider, W. de B. A Pathological Study of the Naturally Acquired Chronic Nephropathy of the Dog, *J. M. Research* **34** 177 (May) 1916.

5 Baehr, George. Glomerular Lesions of Subacute Bacterial Endocarditis, *J. Exper. Med.* **15** 330 (April) 1912.

The occurrence of lesions in the kidney is not constant in staphylococcic infections. In cases of renal damage there can usually be found abscesses. The capillary thrombi and glomerular adhesions seem to be most often the result of injury produced by the staphylococcus toxin.

A marked increase in the amount of albumin and the number of red blood cells and hyaline and granular casts in the urine is found only in cases in which there has been damage to the functional unit of the kidney. The absence of edema and the presence of normal blood pressure have been observed in cases of acute glomerular nephritis due to the streptococcus. The degree of damage to the kidney in staphylococcic infections is evidently very slight, it is usually insufficient to produce an elevation in the nonprotein nitrogen content of the blood, however, this may occur, as shown by case 1.

One can readily understand why so little attention has been given to staphylococci as an etiologic agent in glomerulonephritis when the cases here are considered. The amount of blood and albumin in the urine is usually small and is present only for a short time. Evidently glomerulonephritis due to *Staph aureus* occurs only rarely, however, it is suggested that some of the hyaline glomeruli found in the cases in which clinical nephritis is not present may be the result of a previous staphylococcic infection.

The etiology and pathogenesis of the lesions in the kidney may be summarized as follows. In a localized *Staph aureus* infection or in a staphylococcic bacteremia the organisms produce a toxin which injures the endothelial cells. As a result of this damage the permeability of the capillary wall is increased, red blood cells escape into the glomerular space and then pass into the lumen of the tubules. If the injury is severe the endothelial cells swell, become necrotic and fuse with the adjacent cells to form the thrombi which have been described, the damaged capillary loop may become adherent to Bowman's capsule. The epithelial cells lining the renal tubules are injured by the toxin. It is impossible at this time to say whether the toxin is excreted through the glomerulus and damages the epithelium as it passes downward or whether it is brought by the blood to the epithelial cells and injures them directly.

#### CONCLUSIONS

Seven cases of *Staph aureus* infection are reported in which there was either clinical or pathologic evidence of renal damage.

In the cases studied clinically the findings were the same as those in any case of acute glomerulonephritis.

The thrombi in the capillary loops may be the result of necrosis and fusion of endothelial cells and resemble some of the thrombi which Baehr described in the kidneys in cases of subacute bacterial endocarditis.

The presence of red blood cells in the glomerular spaces and in the lumens of the tubules is a constant finding in these cases

Many of the lesions in the kidney resemble those produced experimentally in the rabbit by the intravenous injection of staphylococcus toxin



# AURICULOVENTRICULAR HEART BLOCK DUE TO BILATERAL BUNDLE-BRANCH LESIONS

REVIEW OF THE LITERATURE AND REPORT OF THREE CASES  
WITH DETAILED HISTOPATHOLOGIC STUDIES

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Lesions of the main branches of the bundle of His as a cause of auriculoventricular heart block have not been sufficiently emphasized, although this cause ranks in importance with lesions of the bundle of His itself, such as fibrosis, calcification and gummatous infiltration. The reason for the lack of recognition of the importance of this cause of heart block lies undoubtedly in the paucity of careful histopathologic studies in cases of heart block. Mahaim,<sup>1</sup> whose work is outstanding in this field, in completely reviewing the literature concerning histopathologic studies of the conduction system in cases of complete heart block was able to select only 25 cases, including 4 of his own, in which the studies were complete and entirely satisfactory in all respects. He selected 11 more cases the reports of which showed only insignificant defects and which could be considered relatively satisfactory. All of the other 79 cases reported were not acceptable by Mahaim because of incompleteness of the clinical data or of the histopathologic studies. We accept, however, 3 cases which Mahaim did not include in his lists of entirely or relatively satisfactory cases - We have also searched the literature from Jan 1, 1930, to the last of March 1935, the period since

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From the Georgetown University School of Medicine and the Army Medical Museum

1 Mahaim, I. *Les maladies organiques du faisceau de His-Tawara*, Paris, Masson & Cie, 1931

2 The case of Nagayo (*Ztschr f klin Med* **67** 495, 1909, case 1), which Mahaim lists among the paradoxical cases, should be added to this list. The case of Cohn and Lewis (*Heart* **4** 7, 1912), listed by Mahaim among the cases of complete heart block due to incomplete lesions, while not thoroughly studied, is also relatively satisfactory. We must also add case XI of Mahaim,<sup>1</sup> which he includes in his own series of cases of bundle-branch block, but which was apparently a case of complete heart block with ventricular tachycardia and right bundle-branch block (old terminology), as Mahaim himself states

Mahaim's study, and can add only 7 cases<sup>3</sup> to the list.<sup>1</sup> Thus the total number of cases acceptable to Mahaim and to us is 48, including the first 2 cases of this report.

In order to make a complete study of the conduction system, serial sections must be made not only of the auriculoventricular node and bundle but also of both bundle branches down to the bases of the papillary muscles. Unfortunately, in man the terminal subendocardial ramifications of the branches and the intramyocardial network of the conduction system are almost impossible to recognize, although from the studies of animals it is known that such extensions exist. In many cases it may suffice to mount and stain only every twentieth section when the sections are 10 microns thick, but in some cases it is advisable to mount and stain every tenth or fifth section or even every section. In the average case 5,000 or 6,000 sections are cut. Much experience is required before one can make reliable studies and draw tenable conclusions.

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3 (a) Yater, W. M. Congenital Heart-Block. Review of the Literature, Report of a Case with Incomplete Heterotaxy, the Electrocardiogram in Dextrocardia, *Am J Dis Child* **38** 112 (July) 1929. (b) Yater, W. M., Lyon, J. A., and McNabb, P. E. Congenital Heart Block. Review and Report of the Second Case of Complete Heart Block Studied by Serial Sections Through the Conduction System, *J A M A* **100** 1831 (June 10) 1933. (c) Yater, W. M., Barrier, C. W., and McNabb, P. E. Acquired Heart Block with Adams-Stokes Attacks Dependent upon a Congenital Anomaly (Persistent Ostium Primum). Report of a Case with Detailed Histopathologic Study, *Ann Int Med* **7** 1263 (April) 1934. (d) Yater, W. M., Leaman, W. G., and Cornell, V. H. Congenital Heart Block. Report of the Third Case of Complete Heart Block Studied by Serial Section Through the Conduction System, *J A M A* **102** 1660 (May 19) 1934. (e) Grant, R. T., and Camp, P. D. A Case of Complete Heart Block Due to an Arterial Angioma, *Heart* **16** 137 (July) 1932. (f) Don, C. S. D., Grant, R. T., and Camp, P. D. A Case of Complete Heart Block with Varying Ventricular Complexes, *ibid* **16** 145 (July) 1932. (g) Yater, W. M., and Cornell, V. H. Heart Block Due to Calcareous Lesions of the Bundle of His. Review and Report of a Case with Detailed Histopathologic Study, *Ann Int Med* **8** 777 (Jan.) 1935.

4 The case of Parade and Voit (*Deutsche med Wchnschr* **57** 629 [April 10] 1931) could probably be added if they had given the details of their histologic technic. The cases of Papp (*Policlinico [sez med]* **39** 252, 1932) and of Rosenthal (*Arch Int Med* **50** 730 [Nov.] 1932), and the numerous ones of Geraudel and his collaborators (*Ann d'anat path* **6** 1075 [Nov.] 1929, *Paris med* **2** 25 [July 5] 1930, *Arch d mal du cœur* **23** 704 [Nov.] 1930, *Ann d'anat path* **8** 339 [April] 1931, *Arch d mal du cœur* **24** 605 [Oct.] 1931, *Ann d'anat path* **9** 715 [July] 1932, *Arch d mal du cœur* **25** 605 [Oct.] 1932, *ibid* **26** 1, 1933) cannot be included because of the apparent incompleteness of the studies. The six cases of Kung and Mobitz (*Arch f exper Path u Pharmacol* **155** 295, 1930) must be excluded also, because the details of the histologic technic are not given and the electrocardiograms are not reproduced. The case of Don, Grant and Camp<sup>3f</sup> is included, although the left bundle branch was apparently not completely studied; the lesion found, however, was sufficient to explain both the auriculoventricular dissociation and the varying ventricular complexes.

Mahaim<sup>1</sup> observed that in practically all cases of established complete heart block in which studies of the conduction system had been made and in which the latter had been pronounced by the investigator to be normal or not sufficiently diseased to produce heart block the bundle branches had not been carefully examined in their entire course. His conclusion from a study of all of the acceptable data was that established auriculoventricular heart block is always due to interruptive organic lesions of the auriculoventricular node or bundle or of both bundle branches, the latter being affected either alone or with the bundle. There are, of course, cases of transient heart block due to toxic depression of the conduction system, as in rheumatic or diphtheritic myocarditis, or to excessive vagal stimulation, as with large doses of digitalis. Geraudel<sup>2</sup> does not agree with this conception of the organic nature of permanent heart block since in most of his cases he did not find serious lesions of the auriculoventricular node or bundle. He did not, however, examine the bundle branches throughout their course although the electrocardiograms in several of his cases indicate that lesions of the bundle branches may have existed.

Of the 48<sup>3</sup> cases of complete auriculoventricular heart block accepted by Mahaim and by us as being satisfactory from the standpoint of the histopathologic examinations and otherwise there were 9<sup>4</sup> in which the bundle branches were interrupted by organic lesions at one or several points and in which the auriculoventricular node and bundle were normal. There were other cases of auriculoventricular heart block in which there were destructive lesions of both bundle branches but in which there were also destructive lesions of the bundle of His. The accom-

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5 This number includes cases 1 and 2 of this report. Case 3 is not included because the heart block was neither permanent nor complete.

6 The case of Hoffmann and Monckeberg (Hoffmann, A. *Die Elektrokardiographie als Untersuchungsmethode des Herzens und ihre Ergebnisse*. Wiesbaden: J. F. Bergmann, 1914; Monckeberg, J. G. *Zur Einteilung und Anatomie des Adams-Stokes'schen Symptomenkomplexes*, *Beitr z path Anat u z allg Path* **63** 99, 1916), described by Mahaim as one of bilateral bundle-branch block, is not so considered by us because the bundle of His was seriously affected as well as the bundle branches. The cases of Waldrop (*Bradyarrhythmie dans une fibrillation auriculaire avec extrasystole cliniquement diagnostiquée, électro et anatomiquement ratifiée* [sic], *nodule calcaire dans la branche droite du faisceau de His*, *Rev Assoc med Argent* **37** 74, 1924), Schmiedl (*Beitrag zur Kenntnis der Adams-Stokes'schen Krankheit*, *Ztschr f Herz u Gefasskr* **5** 393, 1913), Herxheimer and Krohl (*Das Adams-Stokes'sche Symptomenkomplex und das His'sche Bündel*, *Deutsches Arch f klin Med* **98** 330, 1910), Pletnew and Kedrowsky (*Ein Fall von Morgagni-Adams-Stokes'schen Symptomenkomplex*, *Ztschr f exper Path u Therap* **9** 594, 1911) and of Wenckebach and Winterberg (*Die unregelmässige Herzthätigkeit*, Leipzig, Wilhelm Engelmann, 1927, p 349) were probably cases of heart block due to bilateral bundle-branch lesions, but they cannot be included because the reports are all lacking in some important details.

panying table shows the character and seat of involvement of the conduction system in the 48 cases of complete heart block accepted by Mahaim and by us<sup>8</sup>

*The Pathologic Lesions in the Forty-Eight Accepted Cases of Complete Heart Block Studied Histopathologically<sup>4</sup>*

Lesion and Site	Cases
Fibrosis of the A V* bundle with or without involvement of the bundle branches	10
Fibrosis of both bundle branches	9
Gumma of the interventricular septum destroying the A V bundle	7
Calcium mass interrupting the A V bundle	6
Fibrocalcereous lesion of the A V bundle	4
Congenital cardiac anomaly with lack of continuity of the conduction system	3
Ischemic necrosis of the A V bundle	2
Acute diphtheritic inflammation of the A V bundle	1
Aneurysm of the interventricular septum destroying the A V bundle	1
Separation of the A V node from the auricular myocardium by fat	1
Tuberculous myocarditis destroying the A V bundle	1
Primary lymphangio endothelioma of the A V node	1
Fibrosis of the A V bundle in a case of persistent ostium primum	1
Arterial angioloma of the right side of the septum destroying the terminal portion of the A-V bundle	1

\* "A V" represents "auriculoventricular"

7 Footnote 7 deleted by the authors

8 In the following list the cases are distinguished by roman numerals I (a) Luce, H Zur Klinik und pathologischen Anatomie des Adams-Stokes'schen Symptomenkomplexes, Deutsches Arch f klin Med **74** 370, 1902 (b) Fahr Ueber die muskulare Verbindung zwischen Vorhof und Ventrikel (das Hissche Bundel) im normalen Herzen und bei Adams-Stokes'schen Symptomenkomplex, Virchows Arch f path Anat **188** 562, 1907 II (c) Chapmann, W A Case of Cardiac Syphiloma with Bradycardia and Obstruction of the Inferior Vena Cava, the After History and a Post-Morten Examination, Lancet **2** 219, 1906 (d) Keith, A, and Miller, C Description of a Heart Showing Gummatous Infiltration of the A-V Bundle, *ibid* **2** 1429, 1906 III (e) Ashton, T, Norris, G, and Lavenson, R Adams-Stokes' Disease Due to a Gumma in the Interventricular Septum, Am J M Sc **133** 28, 1907 IV (f) Deneke, T Zur Roentgendiagnose seltenerer Herzleiden, Deutsches Arch f klin Med **89** 39, 1907 Fahr<sup>8b</sup> V-VI (g) Bonninger Zwei Falle von Herzblock, Deutsche med Wchnschr **34** 2293, 1908 (h) Monckeberg, J G Untersuchungen uber das Atrioventrikularbündel im menschlichen Herzen, Jena, Gustav Fischer, 1908 VII (i) Volhard, F Ueber die Beziehung des Adams-Stokes'schen Symptomenkomplexes zum Herzblock, Deutsches Arch f klin Med **97** 348, 1909 Monckeberg,<sup>8h</sup> p 120 VIII (j) Gibson, E A, and Ritchie, W T Further Observations on Heart Block, Practitioner **78** 589, 1907, Edinburgh M J **1** 315, 1909, Lancet **1** 833, 1909 IX (k) Pick, E Zur Kenntnis der Adams-Stokes'schen Krankheit, Verhandl d deutsch Kong f inn Med **26** 460, 1909, **30** 511 1913 (l) Koch W Zur pathologischen Anatomie der Rythmusstörungen des Herzens, Berl klin Wchnschr **47** 1108, 1910 X (m) Nagayo, M Pathologisch-anatomische Beiträge zum Adams-Stokes'schen Symptomenkomplex, Ztschr f klin Med **67** 495, 1909, case 1 XI Volhard<sup>8i</sup> (n) Monckeberg J G Zur Einteilung und Anatomie des Adams-Stokes'schen Symptomenkomplexes Beitr z path Anat u z allg Path **63** 77, 1916, p 97 XII (o) Bishop Adams-Stokes Disease with Complete Heart Block Showing a Conspicuous Lesion in the Path of the A-V Bundle, Am J M Sc **139** 62, 1910 (p) Oppenheimer Adele and Oppen-

(Footnote continued on next page)

The following are summaries of the 7 acceptable cases of complete auriculoventricular heart block due to bilateral bundle-branch lesions among the acceptable cases of complete auriculoventricular heart block which have been reported by other authors

1 Deneke and Fahr,<sup>81</sup> 1907 A man, aged 42, had Adams-Stokes attacks for four years. Polygraphic tracings showed complete heart block with a ventricular rate of from 25 to 30 per minute. The heart was dilated, and there was diffuse myocardial fibrosis. The histopathologic study showed fibrosis involving the entire left branch at its origin and fibrosis destroying the right branch at its termination

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heimer, B. S. Three Cases of Adams-Stokes Syndrome, with Histological Findings, *Arch Int Med* **13** 957 (June) 1914 XIII (g) Monrad-Krohn, G. Den atrioventriculære muskel-forbindelse i menneske hjertet (fasciculus atrio-ventricularis), *Christiania, Sten*, 1911 XIV (i) Heilecker, W. Zur Pathologie des Hischen A-V Bündels bei dem Adams-Stokes'schen Symptomenkomplex (und bei Diphtherie), *Frankfurt Ztschr f Path* **8** 319, 1911 XV (s) Falconer, A., and Dean, G. Observations on a Case of Heart Block Associated with Intermittent Attacks of Auricular Fibrillation, *Heart* **3** 247, 1911-1912 XVI (t) Armstrong, H., and Monckeberg, J. Herzblock bedingt durch primären Herztumor bei einem funfjährigen Kinde, *Deutsches Arch f klin Med* **102** 144, 1911 XVII (u) Cohn, A., and Lewis, T. A Description of a Case of Complete Heart Block, Including the Post-Mortem Examination, *Heart* **4** 7, 1912 XVIII (v) Cohn, A., and Lewis, T. Auricular Fibrillation and Complete Heart-Block. A Description of a Case of Adams-Stokes Syndrome Including the Post-Mortem Examination, *ibid* p 15 XIX (w) Griffith, T. Remarks on Two Cases of Heart-Block, *ibid* **3** 141, 1911 (x) Kennedy. Supplementary Note on a Case of Heart-Block with an Examination of the Auriculo-Ventricular Junctional Tissue, *ibid* **6** 37, 1914 XX Oppenheimer and Oppenheimer,<sup>82</sup> case 2 XXI (y) Hoffmann, A. Die Elektrokardiographie als Untersuchungsmethode des Herzens und ihre Ergebnisse, Wiesbaden, J. F. Bergmann, 1914 Monckeberg<sup>83</sup> (1916), p 90 XXII (z) Gaisbock and Jurak. Klinische und anatomisch-histologische Untersuchungen über einen Fall mit Adams-Stokes'schen Symptomenkomplex, *Zentralbl f Herz u Gefässkr* **7** 37 1915 XXIII (a') Biedl, A., and Rühl, J. Ein Fall von Adams-Stokes'schen Krankheit mit Läsionen in beiden Tawara Schenkeln, *ibid* **8** 71, 1916 Monckeberg<sup>83</sup> (1916), p 77 XXIV Mackenzie and Monckeberg<sup>83</sup> (1916), p 105 XXV (b') Bridgman, E., and Schmeisser. Heart-Block Caused by a Gumma of the Septum, *Johns Hopkins Hosp Rep* **18** 90, 1919 XXVI (c') Starling, H. J. Heart-Block Influenced by the Vagus, *Heart* **8** 31 (Feb) 1920 (d') Lewis, T. Post-Mortem Notes of Dr. J. H. Starling's Case of Heart-Block, *ibid* **9** 283 (Dec) 1922 XXVII (e') Waldo, H., and Herapath, C. A Case of Complete Heart Block with Post-Mortem Examination, *Lancet* **1** 271, 1922 XXVIII (f') Sisto, P. Studio clinico ed anatomico-pathologico su di un caso di sindrome di Adams-Stokes, *Malattie d cuore* **6** 6, 1922 XXIX (g') Meyer, P., and Oberling, C. Myocardite tuberculeuse avec syndrome d'Adams-Stokes, *Ann de med* **14** 368, 1923 XXX (h') Kauf, E. Zur Diagnose des Schenkelblocks beim menschlichen Herzen, *Ztschr f klin Med* **98** 126, 1924 XXXI (i') Clarke, N., and Smith, F. Heart-Block of Unusual Etiology, *Am J M Sc* **169** 882, 1925 XXXII (j') Geraudel, E. Un nouveau cas de syndrome d'Adams-Stokes par lésion transverse du ventriculonecteur, consecutive a une stenose de son artere, *Ann d'anat path* **6** 1075, 1929 XXXIII (k') Geraudel, E., Brodin,

2 Gaisbock and Jurak,<sup>87</sup> 1915 A man aged 71, had Adams-Stokes attacks for three years. The pulse rate was from 26 to 32 per minute. Brief attacks of paroxysmal tachycardia followed the Adams-Stokes attacks. Polygraphic tracings revealed complete heart block. The heart was enlarged, and there were severe sclerosis of the coronary artery and myocardial fibrosis. The histopathologic examination showed complete interruption of the left branch at its origin by atrophy and fibrocalcereous replacement and complete destruction of the end of the right branch by the same type of lesion.

3 Biedl and Rühl and Monckeberg,<sup>88</sup> 1917 A youth, aged 19, had Adams-Stokes attacks. The electrocardiogram was that of complete heart block with left bundle-branch block at first and later right bundle-branch block. The ventricular rate was 26 per minute. The condition of the heart was thought by Ghon to be an example of endocarditis parietalis fibrosa; the valves were not involved. The left bundle branch was destroyed in its upper part by subendocardial fibrosis. The subendocardial portion of the right bundle branch was greatly damaged but not destroyed by fibrosis, which involved also the subjacent myocardium. Monckeberg characterized this as a case of bursitis of the conduction system, an example of "*selbständige Pathologie des Atrioventrikular-system*" (an independent pathologic process of the atrioventricular system).

4 Mackenzie and Monckeberg, 1916 (see footnote 8, case XXIV) An old man was known to have had complete heart block with "left bundle-branch block" for three or four years before his death. The heart showed mild valvular and coronary arterial sclerosis. The histopathologic examination revealed destruction of the intramyocardial portion of the right bundle branch by fibrosis. The left bundle branch was involved by intraseptal fibrosis high in its anterior division and lower in its posterior division. Monckeberg considered this to be a case of old rheumatic myocarditis.

5 Sisto,<sup>89</sup> 1922 A man, aged 80, had Adams-Stokes attacks for two months, and congestive heart failure developed. Polygraphs revealed complete heart block with a ventricular rate of 24 per minute. The heart was large, and there was coronary arterial sclerosis with fibrosis of the myocardium. The histopathologic study showed interruption by fibrosis of the left bundle branch near its origin and similar involvement of the right bundle branch at a distance of 6 mm from its origin.

6 Mahaim,<sup>1</sup> 1931 Observation IV A man, aged 59, had Adams-Stokes attacks for eight months. The electrocardiogram revealed complete auriculoventricular dissociation with two different, but in general type similar, alternating

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P., and Lereboullet, J. Étude d'un cas de syndrome d'Adams-Stokes mortel. Necrose transverse du ventriculonecteur par endarterite stenosante de son artere. Arch d mal du coeur **22** 1, 1929 XXXIV (I') Geraudel, E., and Valensi, A. Un cas mortel de syndrome d'Adams-Stokes. Lesion transverse du ventriculonecteur. Endarterite stenosante de son artere, Ann de med **25** 472 1929 XXXV Yater (1929) XXXVI-XL Mahaim<sup>1</sup> (1931), cases I II III IV and XI XLI Grant and Camp<sup>3c</sup> (1932) XLII Don, Grant and Camp<sup>3f</sup> (1932) XLIII Yater, Lyon and McNabb<sup>3b</sup> (1933) XLIV Yater, Barrier and McNabb<sup>3c</sup> (1934) XLV Yater, Leaman and Cornell<sup>3d</sup> (1934) XLVI Yater and Cornell<sup>3e</sup> (1935) XLVII-XLVIII Yater, W. M. Cornell V. H. and Claytor T. Auriculoventricular Heart-Block Due to Bilateral Bundle-Branch Lesions. Arch Int Med, this issue, cases 1 and 2.

9 The old terminology for bundle-branch block is used throughout this paper, since we are not convinced of its incorrectness although it may have to be modified.

ventricular complexes in the form of a bigeminy, giving the picture of "right bundle-branch block" The ventricular rate was 48 per minute, but the pulse rate was 24 per minute The heart was large, and there was aortic and mitral endocarditis with fibrosis of the myocardium The fibers of the auriculoventricular node and of part of the main bundle were found on histopathologic examination to be dispersed by fat<sup>9a</sup> The left branch was completely destroyed high in its course by an old inflammatory lesion The right branch was destroyed at a lower point by fibrosis

7 Mahaim,<sup>1</sup> 1931 Observation XI A man, aged 51, died as a result of congestive heart failure The electrocardiogram showed what Mahaim interpreted as complete heart block with ventricular tachycardia and so-called arborization block with right bundle-branch predominance The heart was the seat of an old mitral endocarditis with old and fresh endocardial lesions and diffuse arteriolar alterations The histopathologic survey showed incomplete disappearance of the left bundle branch in its superior third as a result of endocarditis and arterial fibrosis There were repeated necrotic lesions of vascular origin in the inferior two thirds of the right bundle branch with destruction in its terminal portion due to successive vascular lesions

We have studied 3 cases of auriculoventricular heart block due to bilateral bundle-branch lesions The first case to be reported was one of complete heart block due to complete interruption by fibrosis of both bundle branches, apparently the result of sclerosis of the large coronary arteries In the second case the patient was observed through all of the stages from sinus rhythm to complete heart block, with the electrocardiographic picture of "right bundle-branch block" existing before and during the phase of partial auriculoventricular block There was severe fibrosis of the left bundle branch with moderate fibrosis of the right bundle branch, due apparently to arteriosclerosis of the small coronary arteries The third patient did not have complete auriculoventricular dissociation permanently, but there were periods when partial heart block existed, periods when complete heart block was present and other periods when there was sinus rhythm There were variable ventricular complexes, usually suggestive of "right bundle-branch block" The etiology lay apparently in periaventricular fibrosis of the small coronary arteries associated with mild myocardial fibrosis

#### REPORT OF CASE 1<sup>10</sup>

*Clinical Record*—A judge, aged 65 at the time of his death, had had considerable dyspnea on exertion for thirteen months Three months before death he had consulted a physician because of severe laryngitis and was found to have a very slow pulse About two months before death, while taking an early morning walk, he suddenly lost consciousness for a few moments and fell to the street He was put to bed and kept there, although he did not experience discomfort His habits had been sedentary He was accustomed to smoke four or five cigars daily but did not consume alcohol He had measles, mumps and pneumonia

9a We do not consider this significant in the production of the auriculoventricular dissociation

10 The subject was a patient of Dr Charles W Barrier of Fort Worth, Texas

in childhood. A year before death he was rejected for life insurance because of an irregular pulse. He had complained of dizziness and "blind spells" occasionally for a year. Physical examination disclosed nothing of importance except moderate cardiac hypertrophy, a pulse rate of 30 per minute and a blood pressure of 160 systolic and 60 diastolic. A fluoroscopic examination did not add any information. He was kept under observation for one month before death. Saturation with oxygen, atropinization and large doses of barium chloride and of thyroid extract at different times did not alter the ventricular rate. Electrocardiograms made at

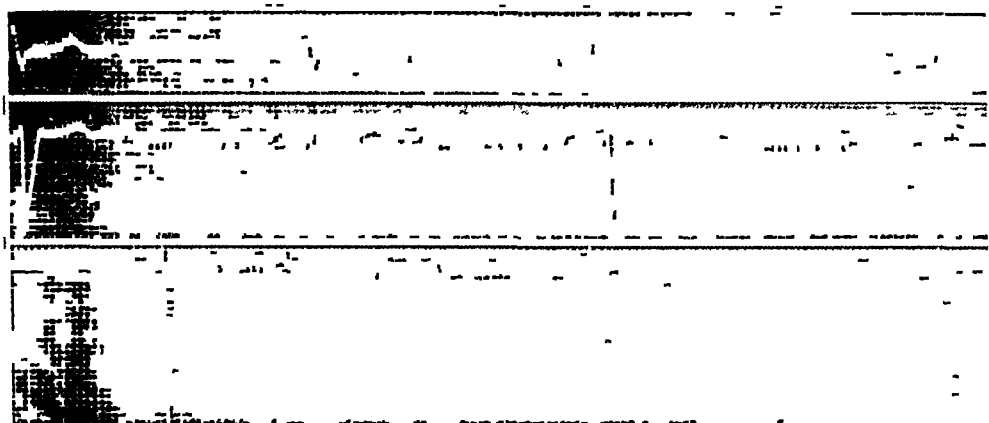


Fig 1 (case 1) —Electrocardiogram showing complete heart block with slurring of the QRS complexes, deep S waves in leads 2 and 3 and an inverted T wave in lead 3



Fig 2 (case 1) —Lead 1 of four electrocardiograms showing absence of effect on the ventricular rate of (a) saturation with oxygen, (b) atropinization, (c) administration of barium chloride and (d) thyroxinization. In c there is an aberrant ventricular complex. Minor variations in the ventricular complexes are frequent. The P wave is occasionally premature and inverted ( $P_1$ ,  $P_2$ )

different times all showed complete heart block. The auricular rate varied from 60 to 100, the ventricular complexes were mainly of the so-called supraventricular form with some slurring of the QRS complexes, deep S waves in leads 2 and 3 and an inverted T wave in lead 3 (fig 1). In one of the electrocardiograms an abnormal ventricular complex replaced one of the complexes of usual form, and minor variations were present even in these (fig 2).



While under observation the patient was subject to attacks of weakness and faintness during which the pulse rate dropped to 20 per minute. Eleven days before death he had an attack of unconsciousness while lying in bed, the pulse rate was 24 per minute. On the tenth day before death Cheyne-Stokes respiration occurred intermittently, the pulse rate remaining 20 per minute. Eight days before death digitalization was begun, and during the remaining period of life dyspnea occurred about every other night, for which morphine was used. In general, the patient felt well. On the day of death (July 23, 1931) he had marked dyspnea and was cold and clammy. The pulse rate was 26 per minute. This attack was recovered from, but later death occurred in an Adams-Stokes attack.

*Necropsy*—There was marked cyanosis of the body. The external jugular veins were greatly distended. There was about 200 cc of clear straw-colored fluid in each thoracic cavity, but the lungs were essentially normal. All of the other organs except the heart were also essentially normal.

*Gross Description of the Heart*—The heart weighed about 450 Gm. The myocardium appeared to be normal. The anterior descending coronary artery was sclerotic, and about 3 cm from its origin it was constricted to about one quarter of its normal caliber. The other coronary arteries were somewhat thickened, but their lumens were of normal diameter. The endocardium and valves appeared normal.

*Histopathologic Examination of the Heart*—Nine blocks of tissue were removed from the auriculoventricular and the interventricular septums. Blocks 1 and 2 included the entire thickness of the septum and contained the auriculoventricular node and bundle and the origins of the two bundle branches. These two blocks were sectioned vertically from behind forward. Blocks 3, 4 and 5 included the marginal trabeculum of the right ventricle and half of the thickness of the interventricular septum. They contained all of the microscopically recognizable right bundle branch below its origin and were sectioned horizontally from above down. Blocks 6, 7, 8 and 9 included almost the entire left side of the interventricular septum (muscular portion) with half of its thickness. Blocks 6 and 7 lay above blocks 8 and 9. These blocks contained all of the microscopically recognizable left bundle branch and were sectioned horizontally from above down. Serial sections, 10 microns thick, were made of all the blocks, and every twentieth section was mounted and stained with Van Gieson's connective tissue preparation. All intervening sections were saved, unmounted and unstained. In all, about 10,000 sections were cut.

The auriculoventricular node and bundle were normal. The artery supplying the node was relatively small and showed very moderate subintimal fibrosis. In the very origin of the left bundle branch there was a small rounded fibrous plaque which did not seem to interfere seriously with the continuity of the branch. Such a plaque should not be considered abnormal for the heart of an older person. Shortly below its origin, however, the left bundle branch began to show dense fibrosis but the subjacent myocardium was relatively normal. The entire width and thickness of the left branch were so affected that few of the conduction fibers were visible in the dense fibrous tissue. This fibrosis was seen in all of the sections containing the left bundle branch, but in the lower half of the septum the fibrosis was not so severe as in the upper half (fig 3). Shortly below its origin the right bundle branch also began to become fibrotic. The fibrosis rapidly became more severe until in the upper third of the branch, which is mainly intramyocardial, there was a small section in which no muscular elements

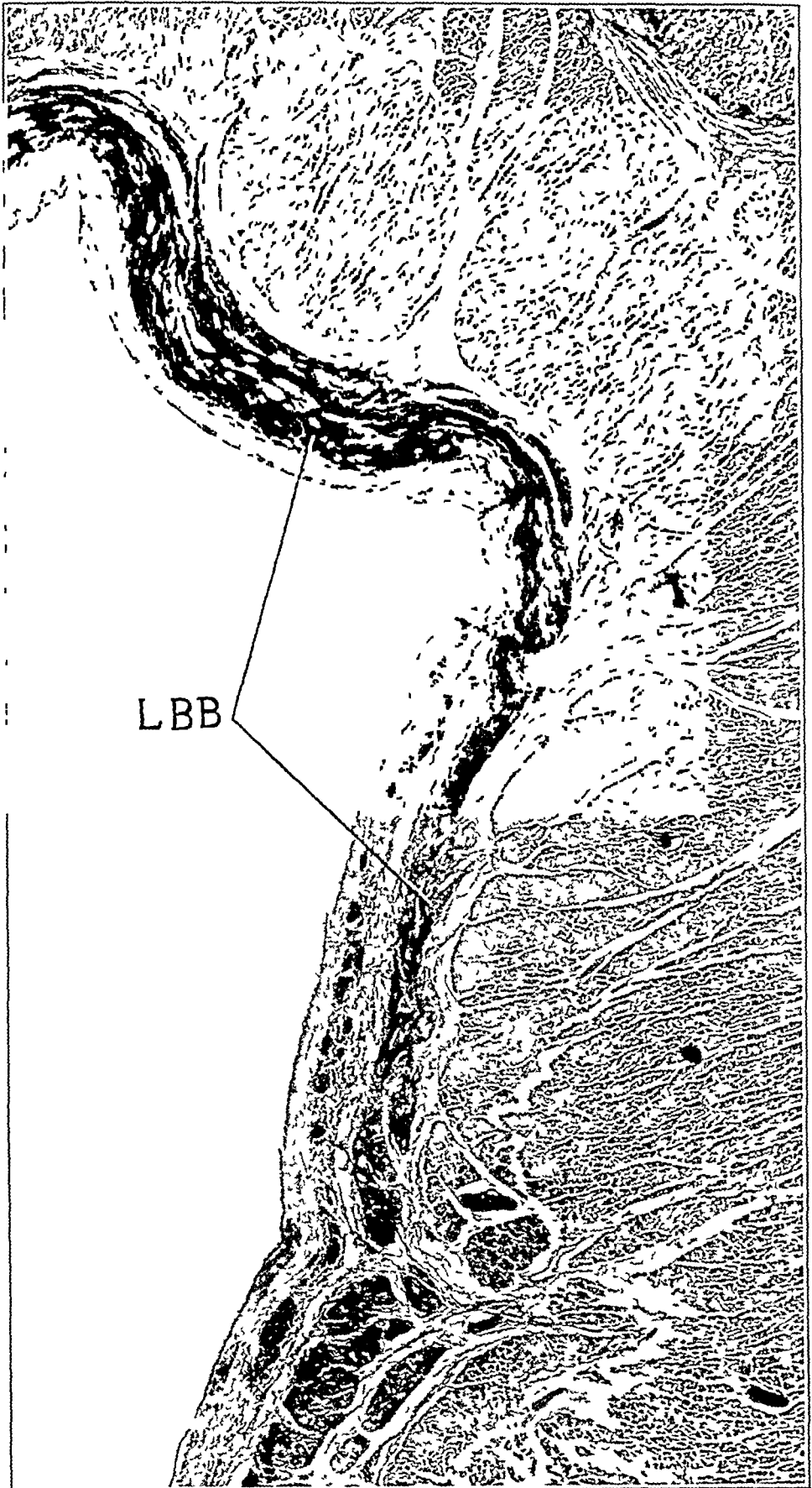


Fig 3 (case 1)—Section 60, block 7, showing fibrous replacement of the left bundle branch, *LBB*, in horizontal cross-section, with normal subjacent myocardium,  $\times 40$

of the branch were visible (fig 4) This fibrosis slowly diminished, and for some distance before the branch became subendocardial it appeared entirely normal again and continued so for the remainder of its recognizable course The myo-



Fig 4 (case 1) —(a) Section 660, block 2, showing moderate fibrosis of the right bundle branch, *RBB*, in oblique cross-section,  $\times 40$  (b) Section 810, block 2, showing fibrosis of the right bundle branch, *RBB*, in horizontal cross-section,  $\times 40$  (c) Section 1020, block 2, showing complete replacement of the right bundle branch, *RBB*, by fibrous tissue, in horizontal cross-section A large vein is seen accompanying the branch at this point,  $\times 40$  (d) Section 440, block 3, showing beginning diminution of the fibrosis of the right bundle branch, *RBB*, lower in its intramyocardial portion, in horizontal cross-section,  $\times 40$

cardium surrounding the right bundle branch appeared to be normal, but some of the smaller arteries in the septum were slightly sclerotic

*Summary of Case 1*—A man, aged 65, had had dyspnea on exertion and spells of dizziness, faintness and unconsciousness for more than a year before death. Complete heart block was known to have existed for three months before death, which occurred in an Adams-Stokes attack. The heart was moderately enlarged, and the coronary arteries were sclerotic, but the myocardium appeared grossly to be normal. Serial sections through the conduction system showed dense fibrosis with practically complete destruction of the whole upper half of the left bundle branch and moderate fibrosis of the lower half. The right bundle branch was also completely destroyed by fibrosis in its upper third and partly replaced by fibrous tissue in its middle third, but its lower third was normal. The myocardium was microscopically essentially normal throughout.

#### REPORT OF CASE 2

*Clinical Record*—A business man, aged 63 at the time of death in 1933, had been a patient of one of us (T A C) since March 1923. His usual complaint was of some minor digestive trouble. He had a severe attack of typhoid fever in his youth and had been treated for a possible peptic ulcer some years before. He had had gonorrhea which had resulted in chronic prostatitis. He used alcohol and tobacco moderately. He led an active life and played golf frequently. He was of a very nervous temperament. Repeated physical examinations had given negative results except for a slightly low blood pressure. While playing golf in June 1929 he fell unconscious but recovered quickly, regaining his feet before his companions could reach him. Physical examination that afternoon was reported to have yielded negative results. A few days after this episode he had a spell of "light-headedness" but did not faint. During August he played golf every day without inconvenience other than that of great fatigue. Early in October he began to have dizzy spells again. A physical examination in December gave essentially negative results. The blood pressure was 110 systolic and 60 diastolic. An electrocardiogram taken Dec 3, 1929 was normal, but the amplitude of the QRS complex was 0.12 second (normally from 0.6 to 0.1 second) and the PR interval was 0.20 second, the upper limit of normal.

Until July 1930 he was free from bad attacks of giddiness but complained of abdominal "gas" and fatigability. A Graham-Cole study of the gallbladder performed in the course of a thorough investigation showed it to be probably pathologic, but operation was not performed. In the latter part of July 1930 he lost consciousness momentarily, and at this time his wife noted that his pulse rate was 52 and the rhythm regular. A short time later his pulse rate was 60, and the next day it was normal. The cardiac examination gave normal results. On August 1, while shaving on a train, he became faint and dizzy and remained so during the day. That night he fainted, and his pulse rate was noted to be 28. For the next five weeks he felt very ill (weak and dizzy), and the pulse rate ranged from 24 to 38. On September 4 the pulse rate reached 50 for the first time. The physician treating him at that time (he was away from home) gave him a hypodermic injection of 12 minims (0.74 cc) of 1:1,000 solution of epinephrine hydrochloride. Most alarming symptoms followed. There was violent trembling, his head felt as if it would burst, the dizziness became severe, his pulse rate rose rapidly to 80 and then dropped to 20, there was gasping for breath, and he felt that he was dying. On September 20 an electrocardiogram showed typical "right bundle-branch block" (old terminology) except that the T wave

was in the same direction as the QRS complex in lead 3. The heart sounds at this time were faint and distant, and a soft systolic murmur was audible over the precordium, but the heart was apparently not enlarged. An electrocardiogram taken on November 3 was similar to that made in September, but a short period of partial auriculoventricular block was disclosed, with an aberrant ventricular complex of extrasystolic form preceding each usual complex during the period of block (fig 5). For the next few months the pulse rate was very irregular, ranging from 32 to 70. The administration of atropine and barium chloride gave no relief but seemed to cause the formation of more "gas." Dyspnea on exertion was noted. An electrocardiogram made on December 10 was essentially the same as the one made in November, with minor differences in the QRS complexes, but one made on Jan 7, 1931 showed a definitely established 2 to 1 auriculoventricular block. At this time, however, the ventricular complexes were

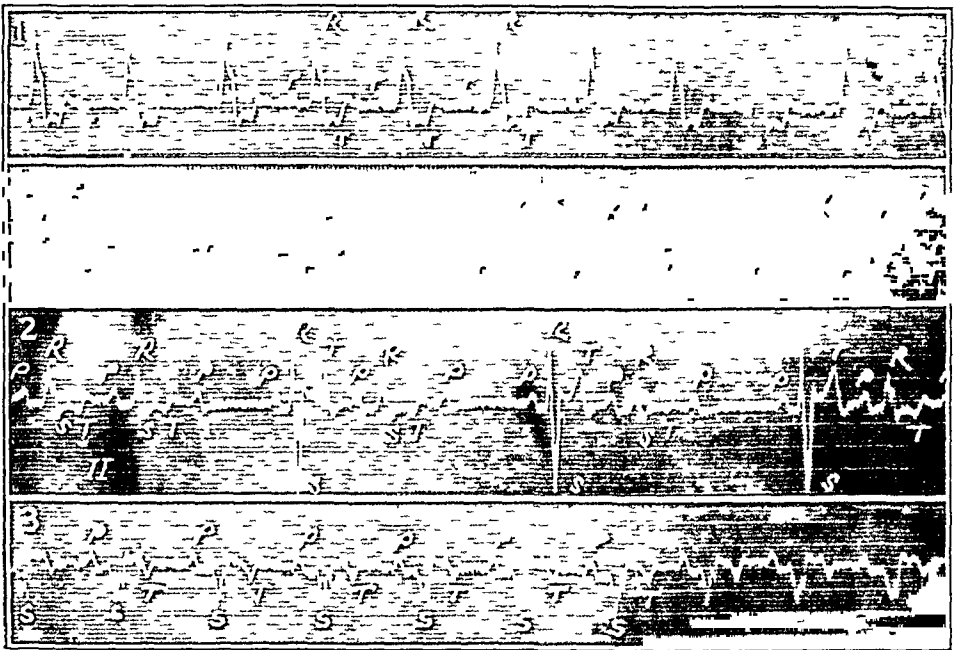


Fig 5 (case 2) —Electrocardiogram showing "right bundle-branch block" (old classification), typical except for inversion of the T wave in lead 3. The duration of P R was 0.24 second, of Q R S, 0.12 second. In the second strip of lead 2 there is a period of 2 to 1 heart block during which there is an aberrant ventricular complex of extrasystolic form preceding each usual complex.

essentially normal, without notching but with some spreading of the QRS complexes (0.1 second in lead 1, 0.12 second in leads 2 and 3), and the T waves were upright. An electrocardiogram made on April 18 was similar except for inversion of the T wave in leads 2 and 3 and a moderately high ST segment in these leads. After the development of the constant 2 to 1 block the course was fairly satisfactory until July 12, when, at the country club, he had a severe spell of repeated attacks of dizziness and faintness lasting for four hours. The face paled, the pulse ceased for varying lengths of time, and the muscles twitched slightly. Ephedrine ( $\frac{3}{8}$  grain [0.02 Gm]) seemed to afford some relief. After the attack he was again fairly comfortable, was able to be driven about in an automobile, walked short distances, and transacted some business over the tele-

phone An electrocardiogram made on Dec 16, 1932, was very similar to that of April 18, 1931, but the T waves in leads 2 and 3 were more deeply inverted, and the S T segment was iso-electric (fig 6)

On Jan 1, 1933, after being on his feet rather too long at a social gathering, he had another setback and had to go to bed for about two weeks On January 21 he became very ill with almost continuous convulsive seizures for forty-eight hours, the pulse at times being as low as 10 per minute and the respirations down to 8 This condition was considerably relieved by the oxygen tent, which was used for about one week During the period of continuous convulsions there was evidence of edema of the lungs with basal râles and bloody expectoration An electrocardiogram made on January 27 showed that an independent ventricular rhythm had been established, with low voltage, notched QRS complex of 0.12 second, prolonged S T interval and inverted T wave in leads 2 and 3 For some weeks he did not have syncopal attacks, but from this time on he was delirious

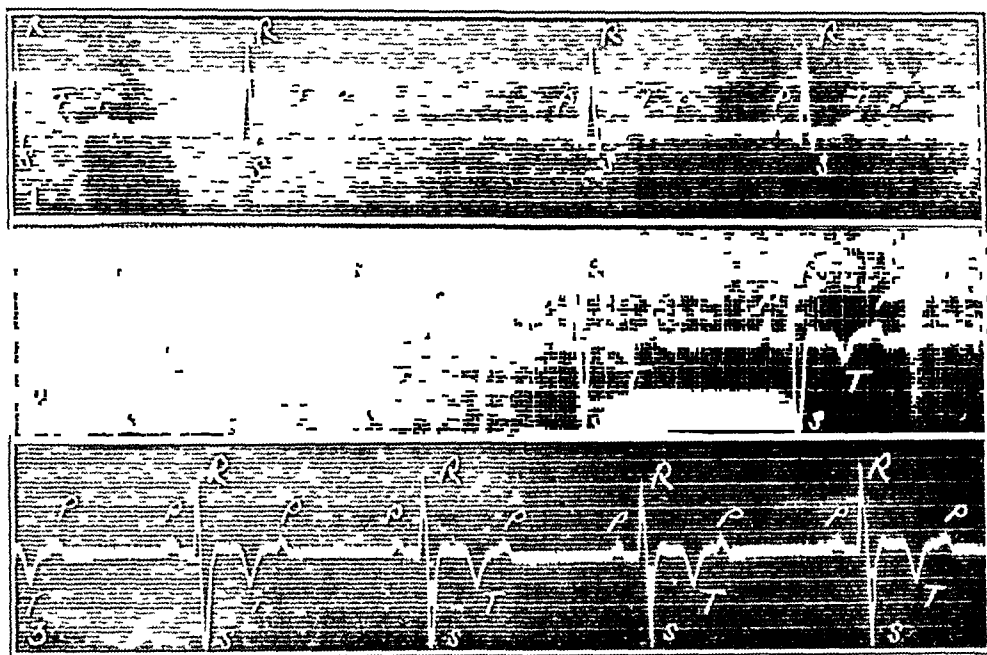


Fig 6 (case 2)—Electrocardiogram showing established 2 to 1 heart block PR equals 0.24 second, QRS, 0.14 second In lead 1 there is transient sinoauricular block There is inversion of the T wave in leads 2 and 3

the greater part of the time The most distressing symptom was Cheyne-Stokes breathing, from which he had no relief except while under the effects of morphine The last electrocardiogram, made on April 6, showed persistence of complete block, but the voltage was no longer as low as before, and the picture again suggested "right bundle-branch block" (fig 7) The blood pressure, which had always been relatively low, became variable during the last illness, ranging as high as 220 systolic, with a relatively low diastolic pressure of from 65 to 80 All of the drugs which have been found to give relief in other cases of heart block, such as barium chloride, atropine, epinephrine, ephedrine, etc, were tried at various times, but none except ephedrine seemed to have any good effect and that only to a small degree On April 11 the convulsions and periods of unconsciousness started again The pulse stopped at times for five minutes, according to the nurse The condition became desperate The temperature rose to 104 F, and death occurred on April 13, almost four years after his first attack on the golf links

*Gross Description of the Heart*—Examination of the heart only was permitted. It weighed 450 Gm. The epicardial fat was normal in amount. The epicardium appeared normal except for some roughening on the anterior surface of the right ventricle in an area about 1 cm in diameter. After being opened in the usual manner the chambers were seen to be normal in size and not dilated. The endocardium and valves appeared to be entirely normal. The myocardium showed no evidence of fibrosis on tangential section. The root of the aorta was smooth. The coronary arteries were not atheromatous or thickened, and their lumens were normal. The left coronary artery supplied more of the myocardium than usual, its circumflex branch extended around to the posterior interventricular sulcus and gave off the posterior as well as the anterior descending branch. The right coronary artery was about half normal in size and consisted only of a circumflex branch and some marginal branches. The endocardium of the interventricular septum on the left side was yellowish but did not appear different from that of most hearts in this respect.

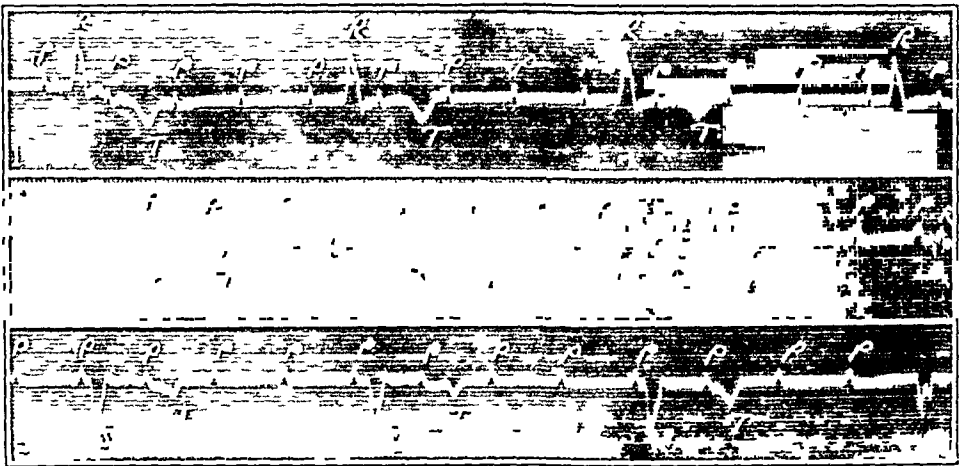


Fig 7 (case 2)—Electrocardiogram showing established complete heart block, the auricular rate being 110 per minute, the ventricular 30. QRS equals 0.12 second. There is inversion of the T wave in all leads. The ST interval is greatly prolonged. Left ventricular preponderance is shown.

*Histopathologic Examination of the Heart*—Four main blocks were removed which included the greater part of the auriculoventricular and the interventricular septums. The largest of these blocks contained the auriculoventricular node and bundle and the origin of the bundle branches. To facilitate fixation this block was divided vertically into nine blocks of equal size (numbered from 1 to 9 inclusive). These blocks were sectioned vertically from behind forward so that the conduction system could be followed progressively from its origin. The other three blocks included the muscular part of the interventricular septum and were designated A, B and C from above down. These contained the bundle branches as far down as they could be followed. These blocks were sectioned horizontally from above down. Another block was removed posterior to the large first block and contained all of the artery to the auriculoventricular node up to the part included in the large block. This block was sectioned vertically from behind forward. All of the blocks were embedded in paraffin, and serial sections of 10 microns of thickness made. Every fifth section of most of the nine small blocks was mounted and

stained Every fifth section of block A and every twentieth section of the other blocks were mounted and stained Van Gieson's connective tissue stain was employed In all, about 4,000 sections were cut All sections not mounted and stained were preserved

The artery supplying the auriculoventricular node was very large Its lumen was good throughout Its wall was moderately thickened owing to subintimal fibrosis A large collar of fat accompanied this artery from the auriculoventricular

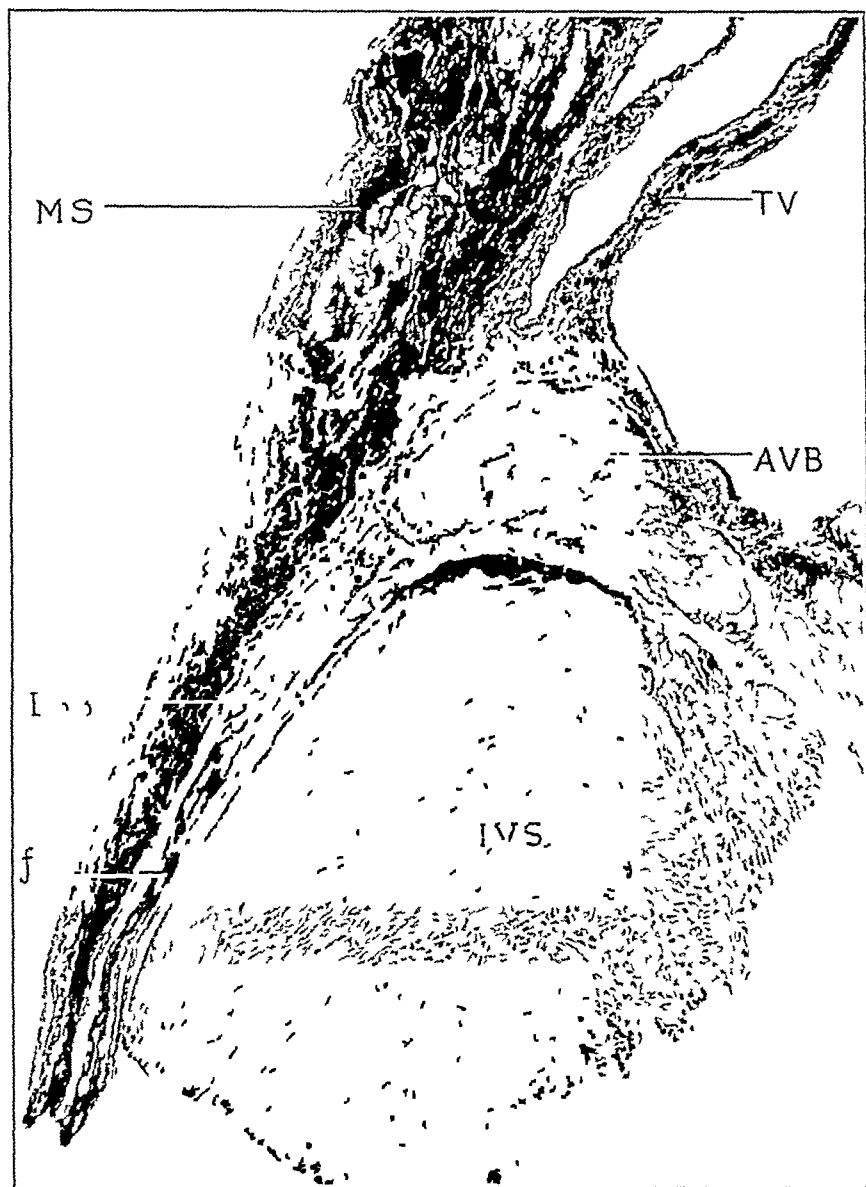


Fig 8 (case 2) —Section 25, block 7, showing the essentially normal bundle of His, *AVB*, in vertical cross-section, and the upper portion of the left bundle branch, *LBB*, with severe fibrosis *f* *MS* indicates the membranous portion of the interventricular septum, *TV*, the tricuspid valve, and *IVS*, the muscular portion of the interventricular septum,  $\times 40$

sulcus into the auriculoventricular septum, and this fat more or less surrounded the subendocardial border of the node The fibers of the node were still united to the auricular myocardium at scattered points through the fat tissue This is a common finding in the hearts of patients of middle life or old age The auriculo-



ventricular node and bundle were histologically normal except for a moderate increase in fibrous connective tissue in the distal portion of the bundle. This connective tissue formed more or less definite fibrous trabeculae between the muscle fasciculi, but there was no destruction of the muscle. Just below its origin the left bundle branch was seen to contain dense fibrous tissue (fig 8). This fibrous tissue extended throughout the entire breadth of the left bundle branch and was confined to it, the subjacent myocardium being free from an abnormal amount of fibrous

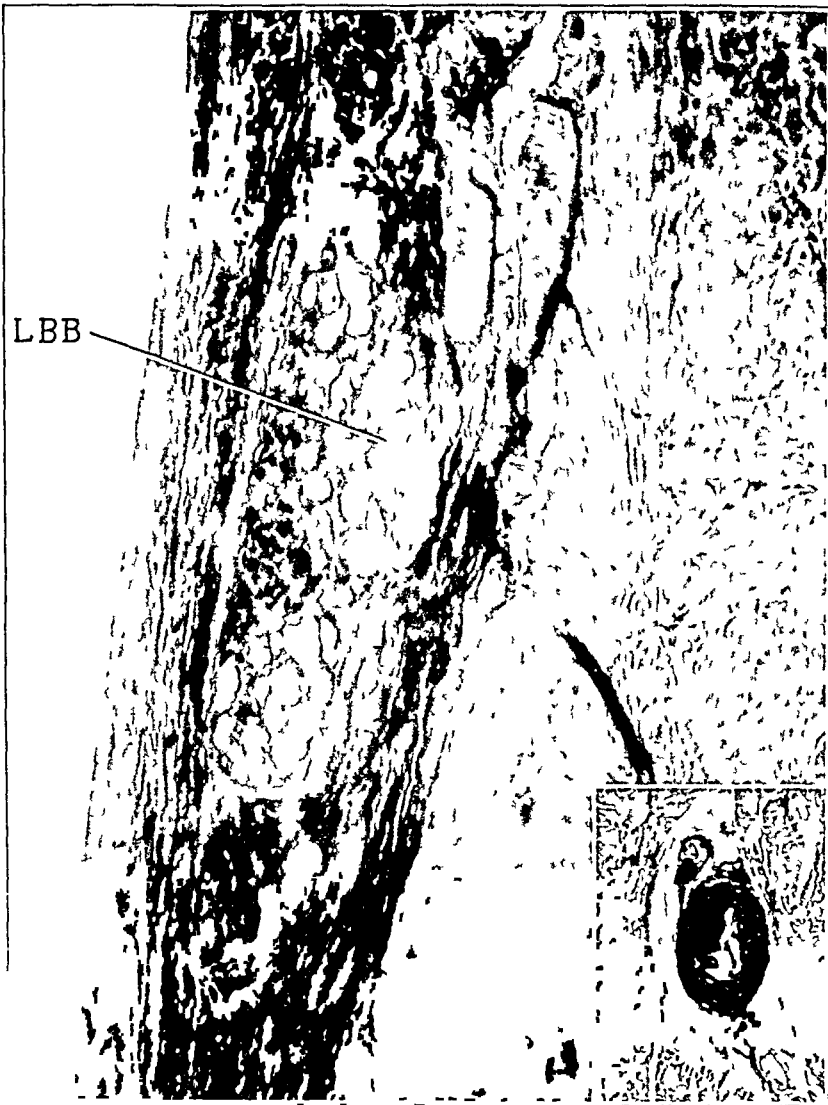


Fig 9 (case 2) —Section 190, block 7, showing marked fibrosis of a portion of the left bundle branch, *LBB*, in vertical cross-section, with the subjacent myocardium relatively normal,  $\times 135$ . The inset shows a sclerotic small artery of the interventricular septum,  $\times 40$ .

tissue. As the branch was followed down the septum it was found to be practically completely replaced by fibrous tissue in its upper half, except for an occasional small group of Purkinje fibers buried in this tissue (fig 9). In the lower half of the septum the fibrosis of the left branch slowly cleared up so that, except for a small border of fibrous tissue, the branch appeared normal. The

very first portion of the right bundle branch contained somewhat more than the normal amount of connective tissue. As the branch descended and became intramuscular the fibrous tissue increased in amount until about one third of the branch consisted of fibrous tissue (fig 10). This fibrosis was confined to the branch, i. e., it did not involve the adjacent myocardium. As the branch was followed lower the amount of fibrous tissue diminished, and at about the junction of its upper and middle thirds the branch became normal and continued so. Both branches were followed onto the papillary muscles until the Purkinje elements could no longer be recognized with certainty.

The myocardium throughout seemed to be normal, but the small arteries in the interventricular septum were thickened here and there, markedly in places, and the lumen was greatly reduced at these points (fig 9, inset). These arterial changes were most notable about the middle of the septum and were most pronounced nearer the left side.

*Summary of Case 2*—A man, aged 63, had had Adams-Stokes attacks for nearly four years. Electrocardiograms taken at intervals during this period showed numerous changes in the ventricular complexes. Before 2 to 1 heart block was established the form was almost typically that of "right bundle-branch block." After 2 to 1 heart block had become established the electrocardiographic picture of bundle-branch block no longer existed. Finally, complete heart block supervened, with the reappearance of "right bundle-branch block." Death occurred during a prolonged convulsive seizure. The heart was slightly enlarged and appeared grossly normal. The larger coronary arteries were not altered. Serial sections through the conduction system showed fibrosis confined mainly to the bundle branches. The upper half of the entire left bundle branch was almost completely replaced by dense fibrous tissue, the lower half was almost normal. The upper third of the right bundle branch was moderately fibrotic, about one third of its cross-section being replaced by fibrous tissue. The lower two thirds of the branch was essentially normal. The myocardium appeared to be normal, but the small arteries in the interventricular septum were considerably thickened and narrowed in places.

#### REPORT OF CASE 3

*Clinical Record*—The patient, a retired army major, aged 49 at the time of death, had been retired at the age of 35 because of bilateral choroidoretinitis of undetermined cause. He remained well, however, until fourteen months before death, suffering only from poor vision. He then began to have dyspnea on exertion and a smothering sensation when he walked about 10 blocks. He had had the ordinary diseases of childhood, malaria at 19, mumps at 26 and gonorrhea without complications at 29. About two months after the dyspnea began he became dizzy after playing eight holes of golf, rested a couple of minutes and proceeded to play until he reached the eighteenth hole, where he had a second dizzy spell of brief duration. The next night he noticed that his pulse was irregular and slow, the rate being about 40 per minute. He entered Walter Reed General Hospital for examination and treatment, and in the ensuing year was a patient there during five different periods. During this time electrocardiograms were made at varying intervals. These will be considered together later. On the first admission the ocular condition was found to be an inactive choroidoretinitis, and there was moderate retinal arteriosclerosis. Degenerative heart disease was diagnosed on the basis of the electrocardiogram. There was no evidence of chronic passive congestion. On the second admission to the hospital in May 1933, besides the ocular and cardiac conditions, generalized arteriosclerosis and subacute thrombotic occlu-

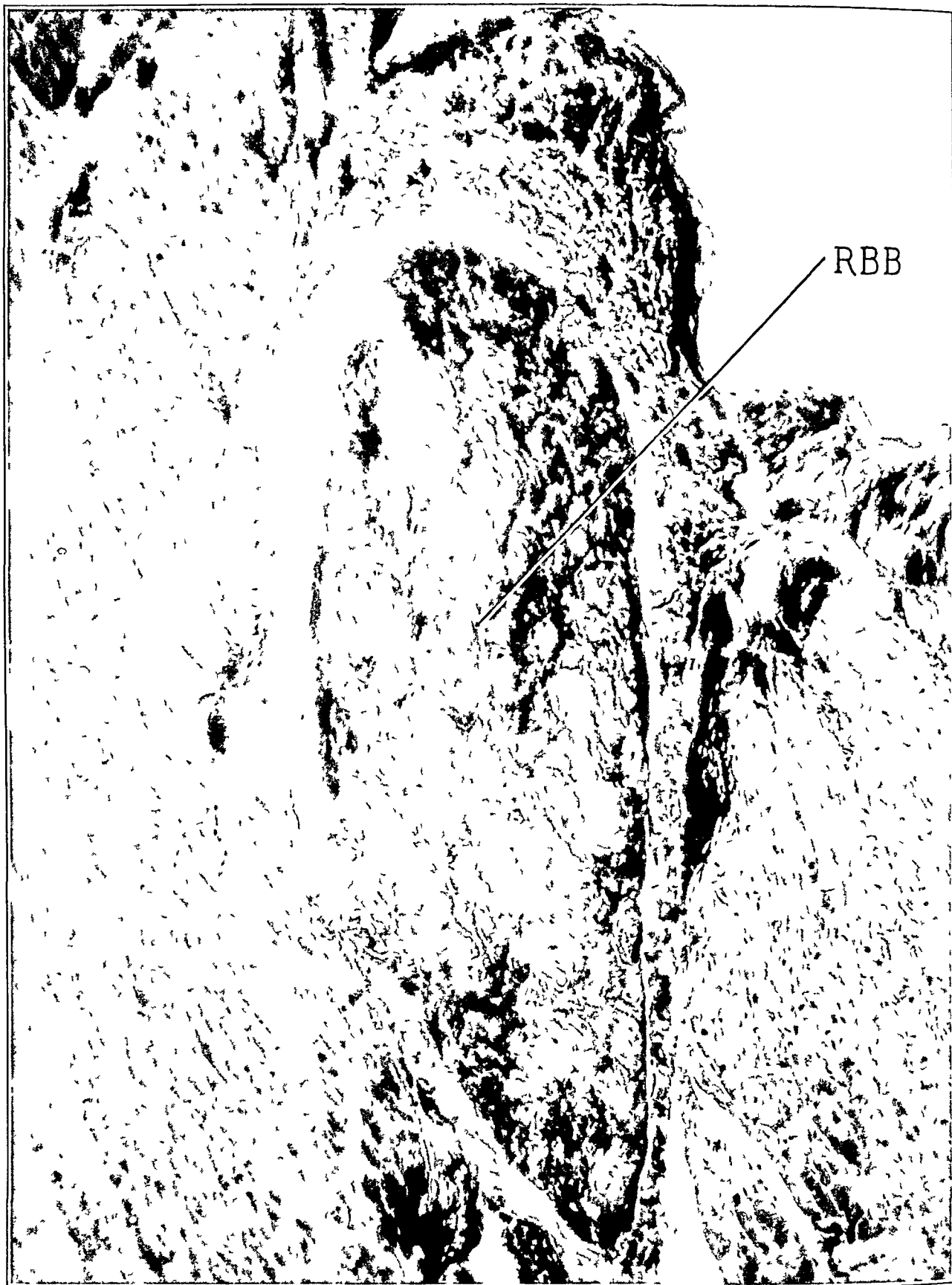


Fig 10 (case 2) —Section 190, block 7, showing the moderately fibrotic right bundle branch, *RBB*, in oblique cross-section, with the surrounding myocardium relatively normal,  $\times 135$

sion of the right posterior tibial artery were diagnosed. The latter progressed, with severe pain, and on the last admission there was early gangrene. Physical examination at this time revealed a fairly well nourished man, prematurely aged. There was great visual impairment. The heart was not enlarged. There was a variable faint systolic murmur, most intense at the mitral area. The ventricular rate was 38 to 42 per minute. The blood pressure in the arms was 132 systolic and 88 diastolic. The lungs were normal. The abdomen was normal. The remainder of the examination revealed nothing of importance except in the right leg and foot, where there was evidence of complete occlusion of the arterial tree from above the popliteal artery, beginning gangrene of the little toe and possible superficial phlebitis of the leg midway between the knee and ankle.

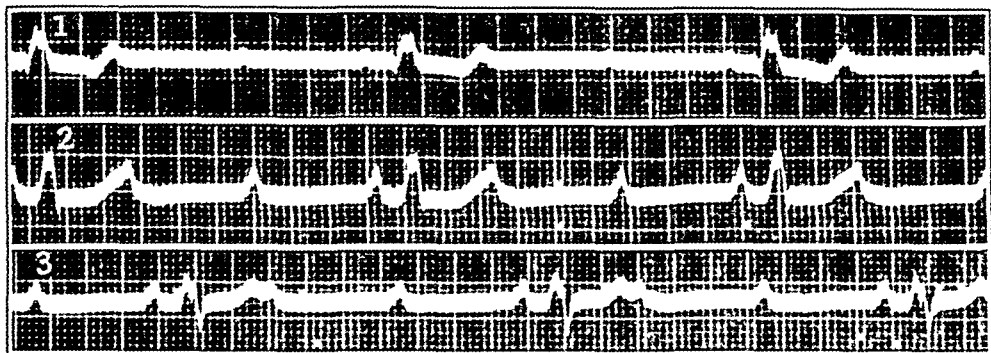


Fig 11 (case 3)—Electrocardiogram made May 23, 1933, showing 3 to 1 heart block and "incomplete right bundle-branch block" (type 1, see text)

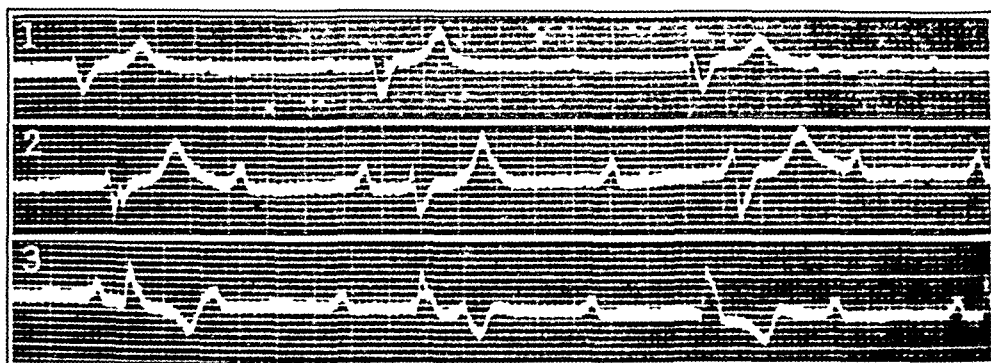


Fig 12 (case 3)—Electrocardiogram made May 16, 1933, showing complete heart block and "left bundle-branch block" (old classification). The QRS complexes vary. QRS equals from 0.14 to 0.16 second (type 2, see text)

Urinalyses, a hemogram, Wassermann and Kahn reactions of the blood and the urea nitrogen of the blood were all normal. Treatment of the vascular condition was begun, and amputation was finally undertaken. Soon after administration of the nitrous oxide and oxygen anesthetic was begun, however, the patient died.

The electrocardiograms made during the year of observation show two main separate and distinct types of ventricular complexes, which changed from time to time from one type to the other. One type was present at the times when there was sinus rhythm or incomplete auriculoventricular block (type 1), the other, when there was complete auriculoventricular block (type 2). Minor changes in the ventricular complexes occurred frequently in both types. The

voltage was moderately low in both. The ventricular complexes of both types were most constant in lead 1. In type 1 (fig 11) the main ventricular complex of lead 1 consisted of the R wave, which was greatly slurred and unaccompanied by Q or S waves, its duration ranging from 0.13 to 0.15 second, its amplitude being never over 6 mm, the T wave was either diphasic or upright, usually the latter. In lead 2 of type 1 the main ventricular deflection was also a very similar R wave with or without a small S wave, the latter varying in size at different times, the T wave was either diphasic or upright, usually the latter. In lead 3 of type 1 the S wave was usually the most prominent part of the ventricular complex, but there was always a small R wave which was notched on its downward slope. The greatest amplitude of the S waves was about 6 mm. The T

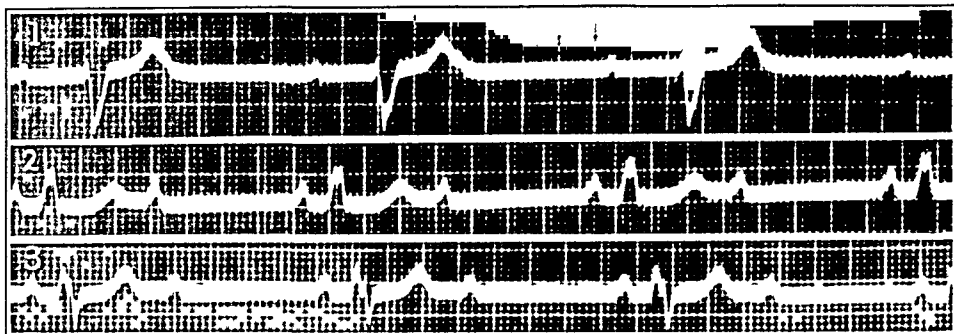


Fig 13 (case 3) —Electrocardiogram made May 22, 1933, showing complete heart block, and "bundle-branch block" intermediate between "right and left bundle-branch block" Q R S equals 0.13 to 0.15 second (type 2, see text)

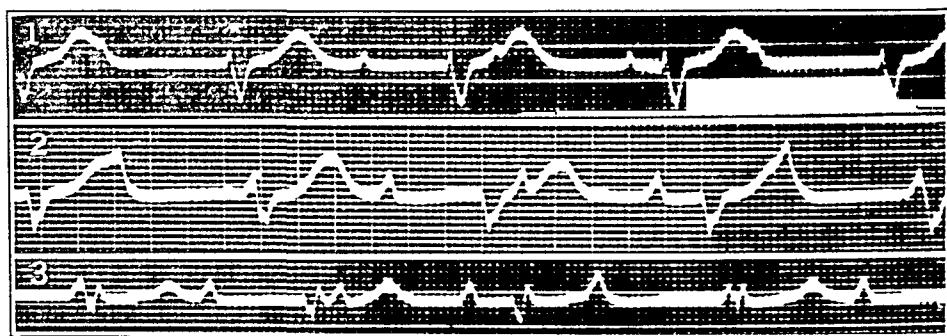


Fig 14 (case 3) —Electrocardiogram made Oct 3, 1933, showing complete heart block and "incomplete left bundle-branch block" (type 2, see text)

wave in lead 3 was always upright. Type 1 might therefore be called "incomplete right bundle-branch block" according to present conceptions or perhaps so-called arborization block of the "right bundle-branch block" form. Type 2 (figs 12, 13 and 14) was more variable than type 1, mainly in leads 2 and 3, but in a general way it presented a picture the opposite of that of type 1, viz, "incomplete left bundle-branch block" or "arborization block" of the "left bundle-branch block" form. The main ventricular deflection in lead 1 was always the S wave, usually accompanied by a small R wave, the S wave was always slurred but of low amplitude and of a duration of from 0.13 to 0.15 second, the T wave was always upright and moderately large. In lead 2 of type 2 the main ventricular deflection was the S wave on three occasions and the R wave on one occasion (as in type 1),

it was always badly slurred or even notched, the T wave was always upright, and when accompanying the S wave it was considerably enlarged. In the first electrocardiogram of type 2 the main ventricular deflection of lead 3 was a badly slurred R wave without Q or S waves, and the T wave was inverted (fig 12). In the second electrocardiogram of type 2 the R and S waves were of the same small amplitude with slurring of the downstroke of the R wave (as in type 1), and the T wave was upright (fig 13). In the third electrocardiogram of type 2 the main ventricular deflection was the S wave unaccompanied by an R wave, and the T wave was upright, in this electrocardiogram the main deflection of all three leads was the S wave, accompanied by upright T waves. In the fourth electrocardiogram of type 2 there were small Q, R and S waves and the T wave was directed upward (fig 14). The following is a brief summary of all of the 1933 electrocardiograms.

1 January 23 Sinus rhythm with short runs of 2 to 1 auriculoventricular block, "incomplete right bundle-branch block" (type 1)

2 January 26 2 to 1 auriculoventricular block, "incomplete right bundle-branch block" (type 1)

3 February 3 Practically identical with no 2

4 February 13 Practically identical with nos 2 and 3

5 May 15 Complete auriculoventricular heart block, "complete left bundle-branch block" except for low amplitude (type 2, fig 12)

6 May 22 Complete auriculoventricular block, mixed "bundle-branch block," lead 1 being of type 2, leads 2 and 3 of type 1 (fig 13)

7 May 23 A 3 to 1 auriculoventricular block, "incomplete right bundle-branch block" (type 1, fig 11)

8 July 11 Complete auriculoventricular block, mixed "bundle-branch block," the main ventricular complex being the S wave in all three leads, the T wave being upright in all leads (type 2)

9 October 3 Complete auriculoventricular block, "incomplete left bundle-branch block" (type 2, fig 14). This electrocardiogram is intermediate in form between nos 5 and 6

10 October 9 A 2 to 1 auriculoventricular block, "incomplete right bundle-branch block" (type 1), similar to nos 2, 3 and 4

11 November 23 Practically identical with nos 2, 3, 4 and 10

12 November 24 Practically identical with nos 2, 3, 4, 10 and 11

13 December 8 Two similar electrocardiograms with sinus rhythm and "complete right bundle-branch block" except for the low voltage and diphasic T wave in lead 1 (type 1), very similar to no 1

14 December 30 Two similar electrocardiograms with 3 to 1 auriculoventricular block and "incomplete right bundle-branch block" (type 1), similar to no 7

The ventricular rate varied during the year from 37 to 72 per minute according to the presence of sinus rhythm or partial or complete auriculoventricular block. The auricular rate varied from 72 to 94 per minute.

*Necropsy* (performed by Major Hugh Mahon, M C, U S Army, pathologist, Walter Reed General Hospital)—Besides the cardiac lesions, which will be described in detail, the main anatomic diagnoses were slight generalized arteriosclerosis, especially of the smaller vessels, mural thrombosis in the terminal portion of the arteriosclerotic abdominal aorta, arteriosclerosis and organized

thrombosis of the vessels of the right leg from the anterior iliac artery to the dorsalis pedis artery, congestion of the internal viscera, pulmonary edema with atelectasis of several lobes, scar, probably arteriosclerotic, in the lower pole of the right kidney, and linear scar of the spleen

*Gross Description of the Heart*—The heart weighed 410 Gm. The myocardium was flabby and grayish red. In the posterior wall of the left ventricle near the apex and close to the septum there was a small scar, 0.8 cm. in diameter, with fine yellowish mottling. In the interventricular septum near the base anteriorly there was also a suggestion of scarring. The coronary arteries appeared normal, with an occasional small, slightly elevated atheromatous plaque. The endocardium and valves were apparently normal. The ascending portion of the aorta was slightly atheromatous.

*Histopathologic Examination of the Heart*—Besides sections from small blocks of tissue from various parts of the myocardium, serial sections were made from blocks which included the whole of the auriculoventricular and interventricular septums. Owing to the fact that numerous incisions had been made into the muscular portion of the interventricular septum eight blocks of tissue of various sizes were excised and carefully recorded in diagrams. Block 1 was the largest and included the auriculoventricular node and bundle and about 1 cm. of the first portion of both bundle branches. Serial sections 10 microns thick were cut vertically from behind forward. The serial sections of the remaining blocks were made horizontally from above down. Every twentieth section of each block was mounted and stained with Van Gieson's connective tissue preparation. Later, every fifth section of block 1 was mounted and so stained. In all, about 8,500 sections were cut.

The auriculoventricular node and bundle appeared to be normal. There was questionable increase in the connective tissue of the terminal portion of the bundle. From its very origin the left bundle branch in its entire thickness and breadth was extremely fibrotic, approximately 60 per cent of the conduction tissue having been destroyed and replaced by fibrous tissue (fig. 15). In some places the conduction tissue was totally replaced by fibrous tissue, in others it was embedded in or surrounded by fibrous tissue. This fibrosis was greatest in the first centimeter of the branch. Below that, it rapidly diminished in amount, more rapidly in the posterior division of the branch, until at about the lower edge of the upper third the branch was almost normal. The fibrosis was apparently not the result of endocardial disease but of intrinsic damage. The right branch was also fibrotic from its very origin, but the fibrosis did not reach a maximum degree until about the middle of the intramyocardial portion, i. e., about the middle of the course, where the branch was replaced by fibrous tissue to the extent of about 75 per cent. There were relatively few conduction fibers, and these were embedded in dense fibrous tissue (fig. 16). Below this region the degree of fibrosis rapidly diminished until the branch, still intramyocardial, soon became quite normal and continued so for the remainder of its course. The fibrosis of the branches was confined to them, the surrounding and subjacent myocardium being almost normal. There was slight to moderate generalized increase in connective tissue in the myocardium of the septum, and the fibrous trabeculae carrying the larger arteries in the myocardium were moderately increased in thickness and density. The arteries themselves, however, did not appear to be more than slightly sclerosed. In two of the blocks the anterior descending branch of the left coronary artery was included. This showed some subintimal fibrosis, but the lumen was not diminished in caliber. In the area near the apex of the left

ventricle already mentioned as being scarred there was extensive dense fibrosis without cellular infiltration. Included in the scar were some small islands of fat cells. In sections from other parts of the myocardium the appearance was the same as that of the septum.

LBB

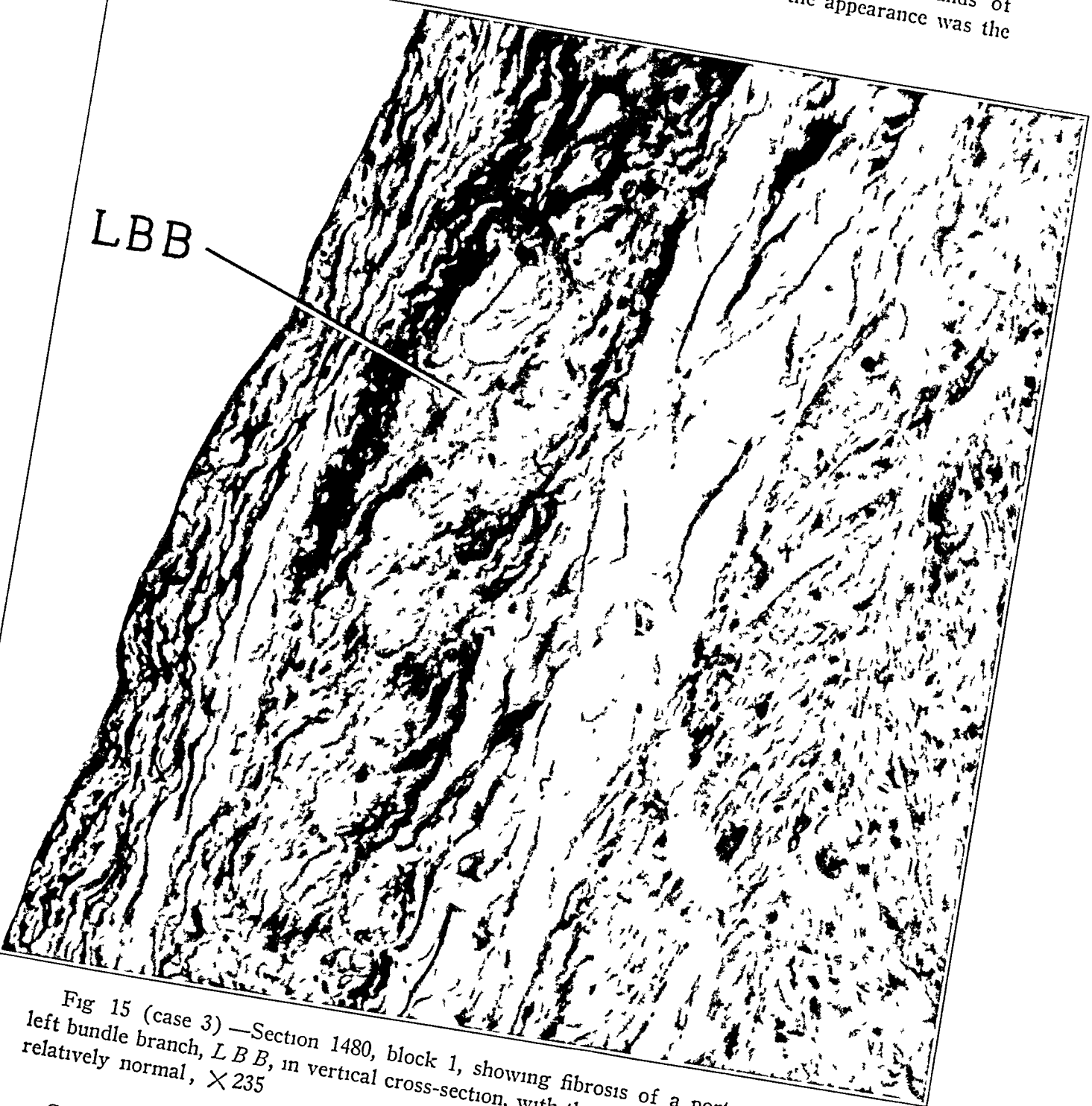


Fig 15 (case 3)—Section 1480, block 1, showing fibrosis of a portion of the left bundle branch, *LBB*, in vertical cross-section, with the underlying myocardium relatively normal,  $\times 235$

*Summary of Case 3*—A man, aged 49, had some dyspnea on exertion and occasional dizzy spells for over a year before death. Thrombotic occlusion of the arteries of his right leg developed, and he died under the anesthetic before amputation could be performed. Numerous electrocardiograms made during the



last year of life showed varying degrees of auriculoventricular heart block with some periods of sinus rhythm. In all of the electrocardiograms there was evidence of impaired conduction of one or the other bundle branch, more often of the

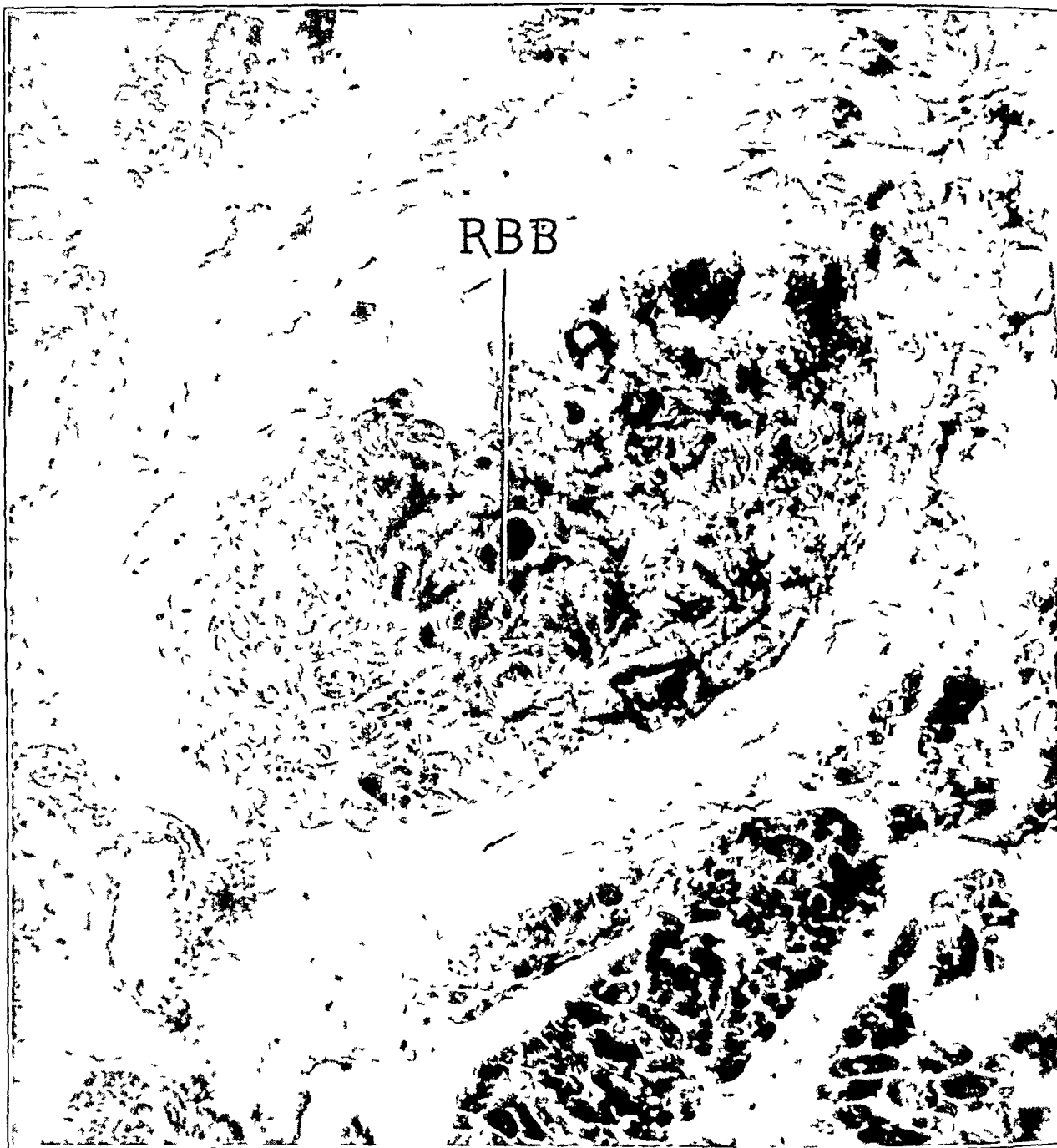


Fig 16 (case 3) —Section 1100, block 3, showing the very fibrotic portion of the right bundle branch, *RBB*, in horizontal cross-section,  $\times 235$

right. The heart was slightly enlarged and was grossly almost normal. Serial sections through the conduction system showed fibrosis confined to the bundle branches, about 60 per cent of the track of the left branch being replaced and about

75 per cent of the cross-section of the right branch. This fibrosis was most marked in the upper third of the left branch, the entire width being involved, and in the middle third of the right branch. There was slight increase of connective tissue in the myocardium with moderate increase in the fibrous tissue of the trabeculae carrying the intramyocardial arteries. The large coronary arteries were only slightly affected. There was a small scar near the apex of the left ventricle.

#### ELECTROCARDIOGRAPHIC ALTERATIONS IN SO-CALLED UNILATERAL BUNDLE-BRANCH BLOCK

Rothberger and Winterberg<sup>11</sup> and later Lewis<sup>12</sup> described the electrocardiographic effects of section of the bundle branches separately in experimental animals (chiefly, the dog). These effects have been repeatedly verified, mainly by Wilson and Herrmann<sup>13</sup> and by Smith<sup>14</sup>. The results were as follows. In lesions of the left bundle branch the chief ventricular deflections of leads 2 and 3 were exaggerated R and T waves, the former directed upward, the latter downward, in lead 1 the deflections were generally of lesser amplitude but similar in direction. In lesions of the right bundle branch the chief deflections of leads 2 and 3 were exaggerated S and T waves, the former directed downward, the latter upward, in lead 1 the first deflection was sometimes upward (R wave), and it was then followed by a downward directed T wave, but more often the deflections were small and directed as in leads 2 and 3.

The electrocardiograms of human beings similar to these descriptions have been thought to represent failure of one or the other bundle branch to conduct (Lewis<sup>15</sup>) and the condition has been designated bundle-branch block. Pure "left bundle-branch block" is supposed to correspond to the dextrocardiogram and pure "right bundle-branch block" to the levocardiogram. Stated otherwise, the electrocardiographic curve is similar to that produced when the left or the right ventricle is stimulated to contract artificially or spontaneously from an ectopic focus (extrasystole).

11 Rothberger, C. J., and Winterberg, H. Zur Diagnose der einseitigen Blockierung der Reizleitung in den Tawara'schen Schenkeln, *Zentralbl f Herzkr* 5 206, 1913, Experimentelle Beiträge zur Kenntnis der Reizleitungsstörungen in den Kammern des Säugetierherzens, *Ztschr f d ges exper Med* 5 264, 1916.

12 Lewis, T. The Spread of the Excitatory Process in the Vertebrate Heart, *Phil Tr Roy Soc, London*, s B 207 221, 1916.

13 Wilson, F. N., and Herrmann, G. R. An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, *Heart* 8 229 (May) 1921.

14 Smith, F. Experimental Observations on the Atypical Q-R-S Waves of the Electrocardiogram of the Dog, *Arch Int Med* 26 205 (Aug) 1920, Further Observations on Experimental Lesions of the Branches of the Auriculoventricular Bundle of the Dog, *ibid* 28 453 (Oct) 1921.

15 Lewis, T. The Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, Ltd., 1920.

The following features of dogs and monkeys were thought to be the same as those of human beings so far as the levocardiogram and the dextrocardiogram were concerned (1) The amplitude of the chief deflection is greater than normal, (2) the initial phases (main ventricular deflections) have an unusually long duration, and (3) the final deflection (T wave) is always opposite in direction to the chief initial deflection. Each curve is, as a whole, broadly diphasic.

Einthoven<sup>16</sup> first showed that the levocardiogram in modified form represents preponderance of the left ventricle and the modified dextrocardiogram preponderance of the right ventricle. The modifications are chiefly that the T wave is not necessarily directed opposite to the chief ventricular deflection. In bundle-branch block the QRS complex is usually of longer duration than in ventricular preponderance, and the main ventricular deflection is often notched. In clinical cases Hyman and Parsonnet<sup>17</sup> have shown that electrocardiographically left or right ventricular preponderance may change to right or left bundle-branch block.

In brief, "right bundle-branch block" is said to deform the ventricular complexes in the direction of the levocardiogram, the left extrasystole or the modified left ventricular preponderance, and "left bundle-branch block," in the direction of the dextrocardiogram, etc. These facts are easy to explain, at least so far as they affect the experimental animal. Section of the right bundle branch bars the passage of the excitation wave which reaches it from the auriculoventricular bundle. The same wave finds the pathway free to the left ventricle, whence the left preponderance. It then reaches the right ventricle by a detour, longer than normal, hence the widening of the electric ventricular group QRS and its abnormal notching. Finally, this deviation consequently produces a parallel deformation of the final ventricular phase (T wave), as if the excitation wave sprang first in the left ventricle, i. e., as in the left extrasystole.

Recently, Barker, Macleod and Alexander,<sup>18</sup> by electric stimulation of the exposed human heart, have thrown doubt on the accuracy of the interpretation as to which is the levocardiogram and which the dextrocardiogram in the case of the human being. They obtained curves exactly opposite to those previously obtained in animals. Later, Wilson,

16 Einthoven, W. Le télécardiogramme, *Arch internat d physiol* **4** 132, 1906, Weiteres über das Elektrokardiogramm, *Arch f d ges Physiol* **122** 517, 1908.

17 Hyman, A. S., and Parsonnet, A. E. Bundle-Branch Block. The Phenomenon of Its Development in Relation to Axis Deviation of the Heart, *Arch Int Med* **45** 868 (June) 1930.

18 Barker, P. S., Macleod, A., and Alexander, J. Excitatory Process Observed in Exposed Human Heart, *Am Heart J* **5** 720, 1930.

MacLeod and Barker,<sup>19</sup> using semirect leads in dogs in which one of the other bundle branch had been severed and the ventricles stimulated separately by an exploring electrode held close to their surface, produced results indicating that the common type of bundle-branch block, formerly called right bundle-branch block, is left bundle-branch block, and that the rare type is right bundle-branch block. Roberts, Crawford, Abramson and Cardwell,<sup>20</sup> in experiments in which they divided the bundle branches in cats' hearts, obtained both concordant and discordant curves in which when the right bundle branch was cut the chief initial deflection was downward in both types, but in lead 3 the deflection was upward in the discordant type. After cutting the left bundle branch, exactly opposite results were obtained. They concluded that in analyzing electrocardiographic curves the important lead to study in order to decide on the location of the lesion is lead 1. In human cases of bundle-branch block Nichol<sup>21</sup> found that in instances of right bundle-branch block the subclavian pulse was definitely delayed, and he concluded that the curves really signified left bundle-branch block. Wilson, Johnston, Hill, Macleod and Barker,<sup>22</sup> by means of serial precordial leads in patients with standard electrocardiographic curves largely similar to those formerly called left bundle-branch block (QRS of 0.12 second or more, narrow R deflections and broad S deflections in lead 1, narrow Q or S deflection in lead 3 synchronous with R of lead 1, and a broad upward deflection in lead 3 synchronous with S in lead 1), obtained curves in which the precordial leads from the right side of the precordium showed a very late chief upstroke and precordial leads from the left side of the precordium showed an early chief upstroke approximately synchronous with the peak of R in lead 1. These curves were strikingly similar to those which they obtained by the same method of leading after section of the right bundle branch in dogs. They concluded that electrocardiograms of the kind mentioned represent right bundle-branch block in man.

Unfortunately, as Mahaim<sup>1</sup> has so well shown, there have been few convincing histopathologic studies made of human hearts in cases in which during life bundle-branch block was thought to exist. In his

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19 Wilson, F. N., Macleod, A. G., and Barker, P. S. The Order of Ventricular Excitation in Human Bundle-Branch Block, *Am Heart J* 7: 305 (Feb) 1932.

20 Roberts, G. H., Crawford, J. H., Abramson, D. I., and Cardwell, J. C. Experimental Bundle-Branch Block in the Cat, *Am Heart J* 7: 505 (April) 1932.

21 Nichol, A. D. The Interpretation of Lead Inversion in Bundle-Branch Block, *Am Heart J* 9: 72, 1933.

22 Wilson, F. N., Johnston, F. D., Hill, I. G. W., Macleod, A. G., and Barker, P. S. The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S-Deflections in Lead 1, *Am Heart J* 9: 459, 1934.

critical review of the literature he found only 19 cases of this kind studied, and of these there were only 3 convincing cases and 1 probable case. In these 4 cases the expected lesions were found (on the basis of the old terminology). Mahaim himself most carefully studied histopathologically 7 cases of clinical bundle-branch block<sup>23</sup> (6 of the right and 1 of the left—observations V, VI, VII, VIII, IX, X and XII) and did not find lesions confined to one bundle branch alone in any. When “right bundle-branch block” was indicated electrocardiographically (observations V, VI, VII, VIII, IX and X) he found destructive lesions of the right branch and also of the anterior division of the left branch. In his single case of “left bundle-branch block” both branches were also involved. In connection with Mahaim’s studies it is interesting to note that Wilson and Herrmann,<sup>24</sup> in an experiment with a dog in which the right bundle branch had been cut and later the anterior division of the left, found that before the latter cut was made the curves for the right branch block were of the concordant type, whereas those obtained after the second cut were of the discordant type and exactly similar to those in Mahaim’s cases of human “right bundle-branch block,” in which both the right bundle branch and the anterior division of the left branch were affected. Rothberger and Winterberger<sup>25</sup> had previously obtained similar curves experimentally in the same way.

Subsequently to Mahaim’s study, Oppenheimer and Oppenheimer<sup>24</sup> presented in abstract the results of studies of 10 cases of clinical bundle-branch block and so-called arborization block. They claimed to have found lesions localized in the left branch in 5 cases of “right bundle-branch block,” in the left branch in 4 cases of “arborization block,” and in the right branch in 1 case of “left bundle-branch block.”

Recently, in a case of so-called arborization block with slight left ventricular preponderance thoroughly studied by Mahaim,<sup>25</sup> he found extensive destructive lesions of both branches. To explain the failure of the appearance of auriculoventricular block he found conduction bundles leading from the upper, uninvolved portion of the posterior division of the left bundle branch and passing inward and downward in the septal myocardium, evidently carrying the impulses from the bundle of His to the ventricles. He concluded that “arborization block” is due to complete destruction of both bundle branches.

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23 We have not included observation XI since this appears to be a case of auriculoventricular block due to lesions of the two bundle branches.

24 Oppenheimer, B. S., and Oppenheimer, E. The Site of the Cardiac Lesion in Ten Cases of Intraventricular Block Including Bundle-Branch Block and Arborization Block, *Tr. A. Am. Physicians* **45** 427, 1930.

25 Mahaim, I. Nouvelles recherches sur les lésions du faisceau de His-Tawara. Le bloc bilatéral manqué, nouvelle forme anatomique de bloc du cœur, à substituer au bloc dit “d’arborisations,” *Ann. de méd.* **32** 347, 1932.

The great discrepancy in all of these works has one main lesson for us, viz, that more thorough and more accurate histopathologic studies are absolutely necessary to settle the questions of "bundle-branch block" and of "arborization block" for clinical cases. Our own experience coincides with that of Mahaim in that lesions of one bundle branch alone are rare. This is not difficult to explain, as will be seen when we come to consider the pathogenesis of "bundle-branch block." We believe that Mahaim<sup>1</sup> has definitely shown that previous conceptions of "bundle-branch block" in the human being were erroneous both as to the histopathologic basis of the electrocardiographic picture and as to the electrocardiographic criteria of bundle-branch lesions.

#### ELECTROCARDIOGRAPHIC ALTERATIONS IN BILATERAL BUNDLE-BRANCH BLOCK

In 1909 Barker and Hirschfelder<sup>26</sup> demonstrated by section of both bundle branches experimentally that complete auriculoventricular dissociation results from this mutilation. Eppinger and Rothberger<sup>27</sup> still more convincingly showed experimentally that transection of both bundle branches causes complete auriculoventricular dissociation, as does interruption of the main stem. Wilson and Herrmann<sup>13</sup> gave added information experimentally for such lesions. Their results were so striking and their conclusions so logical as to make them classic, and we cannot refrain from quoting them verbatim.

We found that in bilateral bundle-branch block the ventricular complex might begin with right ventricular effects, indicating a right-sided pace-maker, it might begin with left ventricular effects, indicating a left-sided pace-maker, or it might be of relatively normal outline as in the instance described by Eppinger and Rothberger<sup>27</sup>. Providing, as we are led to believe, that only the specialized tissues possess the property of rhythmicity in high degree, the normal type of ventricular complex in bilateral bundle-branch block can result only from the simultaneous activity of two pace-makers, one in each branch of the bundle. We cut both divisions of the His-bundle in five experiments. In one of these, the ventricular complexes were of relatively normal form. In the others, occasional changes in the location of the pace-maker from one side to the other occurred, and these shifts were usually accompanied by complexes of transitional form.

The experiments convince us that complete heart block associated with ventricular complexes of varying form is usually due to bilateral bundle-branch block and not to a lesion of the main stem of the His-bundle.

That this is exactly true in cases of actual disease of both bundle branches is amply borne out in human cases in which histopathologic

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26 Barker, L., and Hirschfelder, A. The Effects of Cutting the His Bundle Going to the Left Ventricle, *Arch Int Med* **4** 193 (Oct.) 1909.

27 Eppinger, H., and Rothberger, C. J. Ueber die Folgen der Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems, *Ztschr f klin Med* **70** 1, 1910.

studies have been made. Among the accepted cases of auriculoventricular block which we have already summarized, case 3 was an instance of auriculoventricular block with at first the curve called left bundle-branch block and later that called right bundle-branch block, case 4 showed the curve called left bundle-branch block in addition to auriculoventricular block, case 6 showed the curve called right bundle-branch block with two types of ventricular complexes suggesting two pace-makers in one branch distribution, and case 7 showed abnormal ventricular complexes of the so-called arborization type. In our case 2, after complete auriculoventricular block had become established, the electrocardiogram suggested the origin in one branch, since the curve might be called "incomplete right bundle-branch block" (fig 5). In case 3, whenever auriculoventricular block was present there was variation in the electrocardiographic picture, but in general the tracings were those of "incomplete left bundle-branch block," suggesting, therefore, the site of the pace-maker in the distribution of the other bundle branch (figs 12, 13 and 14).

Although it is probably true that lesions confined to the bundle branches are the usual cause of varying ventricular complexes, there is no reason why destructive lesions of the terminal portion of the bundle of His may not also produce such changes, as is demonstrated well in the case of Don, Giant and Camp,<sup>3†</sup> in which a mass of calcium destroyed the bundle at its bifurcation, and in the somewhat similar case of Yater and Willius.<sup>28†</sup>

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28 In the following list the cases are distinguished by roman numerals. I (a) Monrad-Krohn, G. Le faisceau auriculo-ventriculaire dans le coeur humain, *Arch d mal du coeur* **4** 350, 1911. II (b) Koch, W. Zur Anatomie und Physiologie der intrakardialen motorischen Zentren des Herzens, *Med Klin* **1** 109, 1912. III (c) Mathewson, G. D. Lesions of the Branches of the Auriculoventricular Bundle, *Heart* **4** 385, 1912-1913. IV (d) Oppenheimer, B. S., and Williams, H. B. Prolonged Complete Heart Block, Without Lesion of the Bundle of His and with Frequent Changes in the Idioventricular Electrical Complexes, *Proc Soc Exper Biol & Med* **10** 86, 1913. V (e) Cohn, A. E. A Case of Transient Complete Auriculoventricular Dissociation, Showing Constantly Varying Ventricular Complexes, *Heart* **5** 5, 1913-1914. VI Hoffmann<sup>8†</sup> (1914). Monckeberg<sup>8a</sup> (1916). VII (f) Christian, H. A. Transient Auriculoventricular Dissociation with Varying Ventricular Complexes Caused by Digitalis, *Arch Int Med* **16** 341 (Sept) 1915. VIII (g) Wilson, F. N. A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, *ibid* **16** 1008 (Dec) 1915. IX Biedl and Riehl<sup>8a</sup> (1916). X (h) Robinson, G. C. The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, *Arch Int Med* **18** 830 (Dec) 1916. XI (i) Krumbhaar, E. B. Transient Heart Block—Electrocardiographic Studies, *ibid* **19** 750 (May) 1917. XII (j) Wilson, F. N., and Robinson, G. C. Heart Block. I. Two

Many clinical cases in which no detailed histopathologic studies were made are now on record in which the form of the ventricular complexes in the presence of auriculoventricular block was of the bundle-branch type<sup>28</sup> In a number of these, in tracings made at different times or in the same tracing, there were shifts abrupt or gradual, in the form of the ventricular complexes from the right to the left bundle-branch type or intermediate forms In some of these cases the idioventricular rhythm was rapid, indicating probably an irritative as well as a destructive lesion in the branch from which the impulses originated White and Viko<sup>28m</sup> found that in 154 cases of complete heart block there was electrocardiographic evidence of intraventricular block in 56 per cent In a clinical study of 37 cases Willius<sup>28n</sup> noted similar abnormal ventricular complexes in 43 per cent and varying forms of QRS complexes in 9 cases, "indicating multiple foci of impulse production in the ventricles" Among 35 of 43 patients with complete heart block who were followed, Ellis<sup>28m'</sup> noted "intraventricular block" in 5 and "bundle-branch block" in 3 Scherf and Schott<sup>28h'</sup> had 7 cases of shifting pace-makers in association with auriculoventricular block Coehlo<sup>28o'</sup> mentioned 30 cases of auriculoventricular block in which the ventricular complexes varied from time to time in duration and voltage, he discussed the question whether such modifications are due to changes in intraventricular conduction with a single pace-maker or to changes in the site of the pace-maker, and he concluded that the latter is the case In an analysis of 395 cases of "bundle-branch block," Graybiel and

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Cases of Complete Heart-Block Showing Unusual Features, *ibid* **21** 166 (Jan) 1918 XIII (k) Winterberg, H Beitrag zur Kenntnis der Störungen in der Reizübertragung des menschlichen Herzens und der Anfälle bei Adams-Stokes'schen Symptomenkomplex, *Ztschr f d ges exper Med* **8** 132, 1919 XIV (l) Korns, H M Delayed Conduction Through the Right and Left Branches of the Atrioventricular Bundle, *Arch Int Med* **30** 158 (Aug) 1922 XV Meyer and Oberling<sup>8g'</sup> (1923) XVI (m) White, P D, and Viko, L E Clinical Observations on Heart Block, *Am J M Sc* **165** 659, 1923 XVII (n) Willius, F A A Clinical Study of Complete Heart-Block, *Ann Clin Med* **3** 129, 1924 XVIII (o) Géraudel, E, and Giroux, R Le syndrome d'Adams-Stokes et sa pathogénie, *Presse méd* **34** 258, 1926 XIX (p) Géraudel, E, Bénard, R, and Hillemand, P Un second cas de bradyrythmie ventriculaire par sténose de l'artère du ventriculonecteur, *Arch d mal du coeur* **19** 229, 1926 XX (q) Géraudel, E, Bénard, R, Gautier, C, and Heyman Un troisième cas de bradyrythmie ventriculaire par sténose de l'artère du ventriculo-necteur (syndrome d'Adams-Stokes), *Presse méd* **35** 1129, 1927 XXI (r) Gilchrist, A E, and Cohn, A E Ventricular Complexes in Complete Heart Block, *Am Heart J* **3** 146, 1927 XXII (s) Robb, J S Heart Block Associated with Multiple Ventricular Pace-Makers, *Medical and Surgical Year-Book, Physicians Hospital of Plattsburg*, 1929, vol 1, p 279 XXIII (t) Yater, W M, and Willius, F A Heart Block Showing Multiple Transitions Associated with Convulsive Syncope Report of a Case with Detailed Histopathological Study,



Spiague<sup>28w</sup> found 17 instances of complete and 20 of partial auriculo-ventricular block. In a similar study King<sup>28v</sup> noted the frequent coexistence of "bundle-branch block" and varying degrees of auriculoventricular delay or block. Among 155 cases of "bundle-branch block" there were 36 instances of complete auriculoventricular block, and in 5 of these there was evidence of shifts of the pace-maker from one side to the other.

Gilchrist and Cohn,<sup>28r</sup> in reporting 2 cases of complete auriculoventricular dissociation accompanied by the occasional spontaneous appearance of a succession of complexes, each being intermediate in form as compared with its neighbors and varying in type between the levocardiogram and the dextrocardiogram, stated that it is not justifiable to assume that clinical curves displaying such peculiarities indicate necessarily bilateral organic lesions of the bundle branches since the same effects might as readily be produced by functional depression of conductivity as by digitalis. They pointed out, as did Wilson and Herrmann,<sup>13</sup> that the effect of a lesion which delays without completely interrupting the passage of an impulse through one of the main divisions of the bundle will be an alteration in the ventricular deflection and that this will consist in a shift in the time relations of right and left ventricular effects. By the algebraic summation of levocardiogram and dextrocardiogram in varying time relations to each other, as previously done by Wilson and Herrmann,<sup>13</sup> Gilchrist and Cohn found that it was possible to reproduce the transitional complexes for each of their 2 cases. They concluded

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Am Heart J 4 280, 1929 XXIV Geraudel, Brodin and Lereboullet<sup>81</sup> (1929) XXV (u) Bloom, B, and Perlow, S. Complete Heart-Block Associated with Rapid Ventricular Rate. Report of Two Cases, Am Heart J 5 486 (April) 1930 XXVI (v) Geraudel, E, and Lereboullet, J. Syndrome d'Adams-Stokes a évolution rapide par thrombose de la coronaire droite et de l'artere du ventriculonecteur, Paris med 2 25 (July 5) 1930 XXVII (w) Geraudel, E. Etude électrocardiographique et anatomique d'un cas de syndrome d'Adams-Stokes, Arch d mal du coeur 23 704 (Nov.) 1930 XXVIII (x) Grassberger, A. Klinische, elektrokardiographische und histologische Untersuchung eines Falles von Adams-Stokes'scher Erkrankung, Ztschr f klin Med 112 388, 1930 XXIX (y) Henkel, G. Anfallsweise Störungen der Reizbildung und Reizleitung im menschlichen Herzen, Deutsches Arch f Klin Med 167 244, 1930 XXX (z) Hall, D. Two Unusual Electrocardiograms, Proc Roy Soc Med 24 1512, 1931 XXXI (a') Mohler, H K. Bundle-Branch Block. Its Diagnosis and Relation to Other Cardiac Disturbances, M Clin North America 14 885, 1931 XXXII (b') Padilla, T, and Cossio, P, Jr. Disociacion auriculoventricular a mayor frecuencia ventricular por interferencia de dos ritmos, Semana med 1 1306 (May 14) 1931 XXXIII (c') Carter, E P, and McEachern, D. Recurrent Complete Heart Block. Report of a Case Associated with Transient Bundle-Branch Block and Normal Conduction Between Attacks, Bull Johns Hopkins Hosp 49 337 (Dec.) 1931 XXXIV Mahaim<sup>1</sup> (1931), cases IV and XI XXXV (d') Parade, G W, and Voit, K. Zur Pathologie und Therapie der Adams-

that the most likely explanation consists in a change in leadership of the predominant pace-maker from one side of the heart to the other. We agree with this conception, but we believe also that the site of the pace-maker may change from time to time in the distribution of the same bundle branch, and in addition that after leaving the pace-maker there may be a slight variation in the path of the excitation wave from time to time.

The explanation of the supraventricular form of the ventricular complexes when complete auriculoventricular block is due to interruption of both bundle branches is more open to debate. The complexes in our case 1 might be considered to be more or less of this form (fig 1). It is necessary, according to the theory of Wilson and Herrmann,<sup>13</sup> to assume that there are two pace-makers, one in each bundle branch, generating synchronously impulses which pass with equal facility down their respective arborizations and produce the algebraic summation of exact superimposition of levocardiogram and dextrocardiogram as in normal auriculoventricular conduction. This may be possible, but it seems to us to be improbable. We are inclined to the theory that there is only one predominating pace-maker at any one time, and that when the complexes are of the so-called supraventricular form the impulses from this pace-maker pass rather directly from the pace-maker to the Purkinje network of the opposite ventricle, whereas, when the complexes are of the type of intraventricular block, there is a less direct passage of the impulse from one ventricle to the other. In a somewhat similar way

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Stokes'schen Krankheit, *Deutsche med Wchnschr* **57** 629 (April 10) 1931 XXXVI (e') Geraudel, E. De syndrome de Adams-Stokes, endarterite a tendance oblitérante de la coronaire droite et de l'artere du ventriculo-necteur, *Arch d mal du coeur* **24** 605 (Oct) 1931 XXXVII (f') Geraudel, E, Girard, J, and Simonin, J. Mutilation du faisceau de His au niveau de sa moitié gauche, absence de déformation du ventriculo-gramme, *Ann d'anat path* **9** 715 (July) 1932 XXXVIII (g') Condorelli, L. Schenkelblock durch Läsion des Tawaraknotens, *Verhandl d deutsch Gesellsch f Kreislaufforsch*, 1932, p 292 XXXIX (h') Scherf, D, and Schott, A. Ueber die Ursache des Formwechsels automatischer Kammerschläge beim vollständigen Herzblock, *Klin Wchnschr* **11** 945, 1932 XL (i') Hahn, L. Initiale Querdissoziation mit Adams-Stokes'schen Anfällen bei akutem Myokardinfarkt, *Ztschr f Kreislaufforsch* **24** 129 (March) 1932 XLI (j') Coelho, E. Tachycardie ventriculaire au cours de la maladie d'Adams-Stokes par dissociation auriculoventriculaire, *Arch d mal du coeur* **25** 232 (April) 1932 XLII (k') Elliott, A H, and Nuzum, F R. Bundle-Branch Block with Periods of Normal Intraventricular Conduction. Report of an Unusual Case, *Am Heart J* **7** 680 (June) 1932 XLIII (l') Walser, J, Lenégre, J, and van Bogaert, A. Un cas d'atteinte diffuse du système autonome du coeur, *Arch d mal du coeur* **25** 410 (July) 1932 XLIV Grant and Camp<sup>3e</sup> (1932) XLV Don, Grant and Camp<sup>3f</sup> (1932) XLVI (m') Rosenthal, S R. Branch Arborization and Complete Heart-Block, *Arch Int Med* **50** 730 (Nov) 1932 XLVII (n') Ellis, L B. Studies in Complete Heart Block. II A

we may explain why in our case 2, after the establishment of 2 to 1 auriculoventricular block, the ventricular complexes for a time were of the supraventricular form (fig 6), although previously they were of the "right bundle-branch block type." Here we may assume that every other impulse failed to come through either bundle branch, but that, one branch being more affected than the other, only the one branch conducted the alternate impulses, these impulses, however, passed directly through the septum from the conducting branch and entered the Purkinje network of the opposite ventricle below the point of obstruction in the branch. After the establishment of complete block, of course, the pace-maker undoubtedly resided in one bundle branch below the point of interruption of its continuity. The impulses then apparently passed more indirectly to the Purkinje network of the opposite ventricle (fig 7). In our case 3 we may note also that whenever there was sinus rhythm or only partial auriculoventricular block (fig 3) there seemed to be some delay in the passage of the impulse down one bundle branch (presumably the right on the basis of the old terminology) whereas whenever complete auriculoventricular block existed, the site of the pace-maker was apparently in the same bundle branch below its point of damage (figs 12, 13 and 14), and from there the excitation wave reached the opposite ventricle by a detour.

Our theory has some basis in recent anatomic studies. Cardwell and Abramson,<sup>29</sup> by injections of india ink into the conduction system and subsequently studying the microscopic sections, have demonstrated

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Clinical Analysis of 43 Cases, *Am J M Sc* **188** 225, 1932 XLVIII (o') Coelho, E. Le mécanisme de la variation de forme des complexes ventriculaires dans le block complet du coeur, *Arch d mal du coeur* **25** 695 (Nov.) 1932 XLIX (p') Katz, L. N., Hamburger, W. W., and Rubinfeld, S. H. Partial Bundle-Branch Block, *Am Heart J* **7** 753 (Aug.) 1932 L (q') Friedmann, H. Ein Beitrag zur Frage der Reizleitungsstörung des Herzens bei Diphtherie, *Wien med Wchnschr* **82** 1231 (Sept 24) 1932 LI (r) Natin, I. El bloqueo auriculo-ventricular en la difteria, *Semana med* **2** 865 (Sept 29) 1932 LII (s') Freifrau, A. Ueber einen Fall von wechselnder peripherer Leitungsstörung des Herzens mit wechselnder Form der Kammerkomplexes, *Ztschr f Kreislaufforsch* **10** 337, 1933 LIII (t') Garcia, V. G. Bloqueo de la rama derecha del fasciculo de His, con bloqueo intermitente auriculoventricular, *Progresos de la clín* **41** 368 (June) 1933 LIV (u') Geraudel, E., Laignel-Lavastine, P. M., and Boquien, Y. Un cas d'Adams Stokes, longues pauses ventriculaires, traces de transition entre les deux types de dissociation, *Arch mal d coeur* **26** 1, 1933 LV (v') Pareja, J. M. Periode de restauration supernormale dans une dissociation auriculo-ventriculaire complete, *Arch d mal du coeur* **26** 395, 1933 LVI (w') Graybiel, A., and Sprague, H. B. Bundle-Branch Block. An Analysis of Three Hundred and Ninety-Five Cases, *Am J M Sc* **185** 395 (March) 1933 LVII (x') King, J. T. Bundle-Branch Block. A Case Analysis with Especial Reference to Incidence and Prognosis, *ibid* **187** 149 (Feb.) 1934

29 Cardwell, J. C., and Abramson, D. I. The Atrioventricular Conduction System of the Beef Heart, *Am J Anat* **49** 167, 1931

in the beef heart Purkinje fibers throughout the myocardium, as well as in the subendocardium and in the septal region, apparently connecting the subendocardial network on the two sides of the septum. A similar study with the same result has been made independently by Wahlen,<sup>30</sup> by means of serial sections and reconstruction models after injections of india ink he demonstrated the presence of an intraseptal Purkinje network passing between the two sides of the septum. Although such an intramyocardial network and such a transseptal connection have not been ascertained for the human heart because injections of india ink are not satisfactory and because the Purkinje fibers are too similar morphologically to the myocardial fibers to be recognizable microscopically, it seems logical to assume that such a network and such connections exist. Mahaim<sup>25</sup> claimed to have observed a special pathway of this kind in a human heart, and Géraudel<sup>31</sup> hinted that direct connections exist between the main divisions of the conduction system and the myocardium in human cases. Rothberger<sup>32</sup> has also subscribed to a similar conception. The ventricular complexes will vary, therefore, according to the directness or indirectness with which the excitation wave spreads from its new pace-maker to the opposite ventricle. If the spread is directly through the septum to the Purkinje network of the opposite ventricle the complexes should be of the supraventricular form since both ventricles are activated almost simultaneously, if the spread is indirectly through the septal myocardium the curves should suggest intraventricular block of incomplete bundle-branch form, and if the spread is first through one branch distribution before the other ventricle is activated the curves should suggest more the picture of complete bundle-branch block.

#### PATHOGENESIS OF "BUNDLE-BRANCH BLOCK"

By far the most common cause of bundle-branch lesions is coronary arterial sclerosis<sup>33</sup>. This preponderance is not so great in lesions of the main stem of the conduction system (table). In the pathogenesis of bundle-branch lesions the next most common factor is probably endocarditis extending downward from the aortic or mitral valve to involve

30 Wahlen, B. Die interventrikulären Verbindung im Reizleitungssystem des Herzens, Upsala lakaref. förh. **38** 1, 1932.

31 Géraudel, E., and Gautier, C. Syndrome d'Adams-Stokes par necrose transverse du ventriculo-necteur consecutive a une endarterite oblitérante de son artère, Ann d'anat. path. **8** 339 (April) 1931. Géraudel<sup>8k'</sup> Géraudel and Lereboullet<sup>28v</sup> Géraudel<sup>28w</sup> Géraudel<sup>28e'</sup> Géraudel, Girard and Simonin<sup>28f</sup>

32 Rothberger, C. J. Beitrag zur Kenntnis der intraventriculären Leitungsstörungen und zur Therapie des "Arborisation Block," Ztschr. f. d. ges. exper. Med. **87** 763, 1933.

33 Mahaim<sup>1</sup> Scherf and Schott<sup>28h'</sup> White and Viko<sup>28m</sup> Willius<sup>28n</sup> Ellis<sup>28n'</sup> Coelho<sup>28o'</sup> Graviel and Sprague<sup>28w'</sup> King<sup>28v'</sup>

the left branch, but this cause is rare compared with the arterial etiology, and other causes are still more rare. Of the 21 cases of bundle-branch lesions associated clinically either with auriculoventricular block or unilateral bundle-branch block only which have been accepted by us from the literature as satisfactory from the standpoint of the histopathologic examination, coronary arterial disease was undoubtedly the only etiologic factor in 14, and in several others it was certainly an important factor in addition to endocarditis.

Mahaim<sup>1</sup> has explained well why cases of pure unilateral bundle-branch block must be very rare. The reason lies in the vascularization of the conduction system, which has been studied by several capable investigators.<sup>34</sup> The auriculoventricular node and bundle are supplied with blood almost entirely by one special artery, the ramus septi fibrosi or first posterior perforating artery, which passes forward into the auriculoventricular septum from the origin of the posterior descending or interventricular artery just at the point posteriorly where the two auricles and ventricles meet. In approximately 90 per cent of hearts this is a branch of the right coronary artery while in 10 per cent it is a branch of the left coronary artery, from the posterior extremity of its left circumflex branch, this artery then passing downward as the posterior descending artery. The anterior descending or interventricular artery may give a minor portion of the blood supply of the auriculoventricular bundle, especially in its anterior portion. As a rule, the origin of the bundle branches also takes its main vascularization from this ramus septi fibrosi, but there are numerous variations. The vascular supply of the bundle branches is less positively known than that of the auriculoventricular node and bundle, but there is a general more or less definite arrangement. The arteries arise from the anterior and posterior descending or interventricular arteries and perforate the interventricular septum, passing toward its middle, where they anastomose to a certain extent. The left bundle branch, being spread out over the subendocardial surface of the left side of the septum and divided usually into an anterior and a posterior division or ramification, has its blood supply both from the perforating septal branches of the anterior and from

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34 (a) Hass, G. Ueber die Gefassversorgung des Reizleitungssystems des Herzens, *Anat. Hefte* **43** 629, 1911. (b) Tandler, J. *Anatomie des Herzens*, Jena, Gustav Fischer, 1913. (c) Gross, L. *The Blood Supply to the Heart*, New York, Paul B. Hoeber, Inc., 1921. (d) Mouchet, A. *Les arteres coronaires du coeur chez l'homme*, Paris, Norbert Maloine, 1922. (e) Crainicianu, A. *Anatomische Studien uber die Koronararterien und experimentelle Untersuchungen uber ihre Durchgangigkeit*, *Virchow Arch. f. path. Anat.* **238** 1, 1922. (f) Spalteholz, W. *Die Arterien der Herzwand*, Leipzig, S. Hirzel, 1924. (g) Geraudel, E. *L'artere de l'atrioventriculaire artere du noeud de Keith-Flack*, *Presse med.* **33** 1283 (Sept. 26) 1925.

those of the posterior descending artery. In a general way the anterior perforating arteries supply the anterior division of the left bundle branch, the posterior perforating arteries the posterior division. The vascularization of the right bundle branch, a threadlike fasciculus, is not so definitely known, but is most probably almost entirely derived from the perforating septal arteries of the anterior descending artery except, perhaps, in its terminal portion, which may receive some of its blood supply from the lower posterior perforating arteries. The upper third of the branch is probably supplied mainly by the two uppermost anterior perforating arteries and the middle third by a special branch of the second perforating artery, the *ramus limbi dextri* (Gross<sup>34c</sup>). This same special artery probably nourishes most of the lower third of the branch. The anastomoses between the anterior and posterior perforating arteries are probably very fine and not particularly effective, as has been shown so well by Crainicianu<sup>34e</sup> for sudden obstruction. With slow obliteration these anastomoses are probably more efficacious in maintaining an adequate blood supply than with sudden occlusion.

Thus, it is seen that the blood supply of the auriculoventricular node and bundle and of the posterior division of the left bundle branch comes mainly from the perforating septal arteries of the posterior descending or interventricular artery (in 90 per cent of cases a branch of the right coronary artery) whereas the blood supply of the right bundle branch and of the anterior division of the left branch is almost entirely derived from the perforating septal branches of the anterior descending or interventricular artery.

From these facts it may be deduced that since obliterating vascular disease affects most often and most severely the anterior descending artery, especially high in its course, the right bundle branch and the anterior division of the left branch are simultaneously affected, and more often than other parts of the conduction system, by the resulting reduction of blood supply. The electrocardiographic alterations would therefore be a combination of both right and left bundle-branch effects, as Mahaim<sup>1</sup> has demonstrated. If the posterior descending artery is mainly affected by obliterating vascular disease (a rare event) only the posterior division of the left bundle branch will be seriously undernourished, and there should be only minor alterations of the ventricular complexes. An occlusive lesion of the right circumflex artery (or in an occasional case of the left) might result in fibrosis of the auriculoventricular node or bundle and the origin of the bundle branches with disturbance in auriculoventricular conduction. Obliteration of both the anterior and the posterior descending arteries might result in severe alterations of both bundle branches and therefore in disturbances of auriculoventricular conduction.

Our case 1 is undoubtedly an instance of the latter condition. There was more or less generalized coronary sclerosis, most advanced in the anterior descending artery, but without total occlusion at any point. High-grade fibrosis of both bundle branches resulted. In our case 2 the cause of the fibrotic lesions of both bundle branches was undoubtedly also diminution of the blood supply of the branches, but, in this instance, from widespread sclerosis of the smaller intramyocardial coronary arteries. Case 3 was less definite from the standpoint of etiology, but here again it was probably an instance of vascular disease.

Endocarditis produces disturbance of conduction probably only when aortic or mitral lesions extend to the mural endocardium of the left side of the interventricular septum and involve those portions of the conduction system which are located in the left ventricle. The result would most often be a disturbance of auriculoventricular as well as left bundle-branch conduction, since the bundle of His is most apt to be involved, probably with a portion of the origin of the left bundle branch. It would be rare indeed to have the latter seriously affected without the bundle of His being affected at the same time. In contradiction to these statements it is interesting to note that in Kauf's<sup>51</sup> case of clinical right bundle-branch block the lesion proved to be a fibrous one of the origin of the right bundle branch, although there was rheumatic aortic stenosis with calcification extending from the aortic valve down on to the left side of the septum. Tricuspid endocarditis is so unusual that involvement of the auriculoventricular bundle or the right bundle branch by endocarditis must be extremely rare. Tumors of the heart, which are not common, gummas, fibrous scars and intracardiac aneurysms in the interventricular septum apparently rarely involve a bundle branch sufficiently to interrupt completely its continuity. Three cases of auriculoventricular block have been reported in which the bifurcation of the bundle of His and the origins of the bundle branches were destroyed by fibrocalcaneous lesions and in which electrocardiograms had shown also bundle-branch block with or without varying ventricular complexes (case of Hoffmann and Monckeberg<sup>83</sup>, case of Yater and Wilhus<sup>28</sup>, case of Don, Giant and Camp<sup>34</sup>).

#### MORBID ANATOMY OF THE CONDUCTION SYSTEM

Serious damage of the conduction system may result from coronary arterial disease long before complete occlusion, slow or sudden, produces a myocardial scar or infarct. The ultimate effect of progressive arterial disease on the conduction system is fibrous replacement, just as it is the ultimate result on the myocardium. In our cases 1 and 2 the fibrous replacement was confined to the conduction system, in particular to the bundle branches, and in case 3 the bundle branches were also

seriously affected whereas the myocardium was very moderately involved. This preponderance of involvement of the conduction system over that of the myocardium suggests that the former, like nerve tissue, is more susceptible to reduction of blood supply and anoxemia. The fact that there is a common vascular supply for the conduction system and the myocardium speaks for this conclusion. Other authors have noted this peculiarity, and long ago Monckeberg<sup>35</sup> and Aschoff<sup>36</sup> commented on the limitation of pathologic changes to the conduction system in certain cases. Monckeberg<sup>37</sup> noted that there might be fatty degeneration of the main portion of the conduction system without such involvement of the myocardium and vice versa. Such fatty degeneration of the conduction system does not result in heart block but possibly may cause sudden death<sup>38</sup>. Monckeberg, after studying a case of heart block with fibrosis of the bundle branches, called such a condition "*selbständige Pathologie des Atrioventrikularsystems*"

Wearn<sup>39</sup> demonstrated that the number of capillaries per square millimeter in the conduction system is approximately only half of their number in the ventricular myocardium. This difference may be due to the difference in function of the two tissues, the one the main function of which is contractility requiring a larger blood supply than the one the main function of which is conduction. At the same time, this relative paucity of capillaries in the conduction system may account for the apparently greater susceptibility of this tissue to reduction in blood supply.

Perhaps, in our cases fibrous changes would have developed later in the myocardium if the patients had not died so soon in Adams-Stokes attacks. Perhaps also, if more histopathologic examination of the conduction system were made in cases of degenerative heart disease (hypertensive and arteriosclerotic) lesions would be frequently found even with minor electrocardiographic changes. Death may occur in such cases from congestive heart failure or coronary thrombosis before these changes become so great as to cause serious disturbances of conduction.

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35 Monckeberg, J. G. Zur Pathologie des Atrioventriculärsystems und der Herzschwäche, Berl klin Wchnschr **46** 45, 1909. Monckeberg<sup>8b</sup> cases 67 and 68. Monckeberg,<sup>8a</sup> case 5.

36 Aschoff. Referat über die Herzstörungen in ihren Beziehungen zu den spezifischen Muskelsystemen des Herzens, Verhandl d deutsch path Gesellsch **14** 3, 1910.

37 Monckeberg, J. G. Herzschwäche und plötzlicher Herztod als Folge von Erkrankungen des Atrioventrikulärsystems, Ergebn d allg Path u path. Anat **14** 1, 1910.

38 Nuzum, F. Fatty Infiltration (Lipomatosis) of the Auriculoventricular Bundle of His, with Sudden Unexpected Death, Arch Int Med **13** 640 (April) 1914.

39 Wearn, J. T. The Extent of the Capillary Bed of the Heart, J Exper Med **47** 273, 1928.



## TIME OF ONSET AND DEGREE OF CONDUCTION BLOCK

An interesting problem concerns itself with the question of how soon conduction disturbances occur when the vascularity of the conduction system is reduced. Géraudel<sup>28</sup> expressed the belief that there may be complete inability of the bundle of His to conduct before any organic changes appear. His conclusion is based, however, on incomplete studies, as before mentioned. We do not think that in cases of permanent block of either the auriculoventricular bundle or the bundle branches conduction disturbances occur before there is considerable organic alteration. We do think, however, that serious difficulty of conduction may occur before the bundle or its branches are completely interrupted by organic lesions. This concept is demonstrated by our cases 2 and 3. In case 2 there was only moderate fibrosis of the right bundle branch, yet this bundle apparently did not conduct in its upper third. Parenthetically, this case might be used as an argument by those who have accepted the newer terminology for "bundle-branch block," since there was a large upright R wave in lead 1 and a deep S wave in lead 3 before auriculoventricular block developed, and the left bundle branch was much more seriously damaged than the right. In case 3 there was apparently not complete interruption of either bundle branch yet at times there was complete auriculoventricular dissociation as well as electrocardiographic evidence of "bundle-branch block." In this case it was impossible to say which bundle branch was the more seriously damaged. Nutritional disturbances, toxic depression and vagal influences might each or all affect the remaining apparently healthy portion of the branches and depress their function permanently or paroxysmally more than the organic changes alone would. Both toxic and vagal influences on conduction have been repeatedly observed.<sup>10</sup> These factors would explain the shifts from partial or complete auriculoventricular block to sinus rhythm and back again, as in our case 3, and the paroxysmal auriculoventricular block early in the course of case 2. On the other side of this question are the cases which show that only a few remaining healthy fibers of the conduction system are sufficient to maintain normal conduction.

## SUMMARY AND CONCLUSIONS

1 Three cases of auriculoventricular heart block due to lesions confined to both bundle branches are reported with detailed histopathologic studies. The pathogenesis was probably coronary arterial disease in all.

2 Such lesions of the bundle branches are probably a common, if not the commonest, cause of auriculoventricular heart block.

40 Winterberg, H. Zur Kenntnis und Analyse der periodischen Herztätigkeit beim Menschen, *Ztschr f d ges Exper Med* **10** 113, 1919.

3 The heart may appear grossly normal, with or without gross evidence of coronary arterial disease. The morbid anatomy is usually that of a fibrous replacement which does not necessarily completely destroy the continuity of the bundle branches. Microscopically as well as grossly, the myocardium may appear normal or relatively little affected. This fact indicates that the conduction system is more susceptible to diminution of blood supply than the myocardium is, since there is a common blood supply. If the patient lived longer, similar changes might develop in the myocardium.

4 The freedom of the auriculoventricular node and bundle from similar lesions in such cases is due to the fact that their blood supply comes from a source different from that of the blood supply of the bundle branches and from a portion of the coronary arterial tree less often and less severely affected by degenerative changes.

5 Lesions confined entirely to one bundle branch are apparently rare because of the common source of the blood supply of the right bundle branch and the anterior division of the left bundle branch from the anterior descending artery, which is most often and most seriously affected by degeneration.

6 The form of the ventricular complexes is frequently suggestive of "bundle-branch block," and variation in the form of these complexes is common. These variations suggest a shift in the site of the pace-maker, sometimes from one side of the septum to the other. The ventricular complexes may be of supraventricular form, however, and then there are either two pace-makers, one in each bundle branch, generating impulses simultaneously or, more probably, a single pace-maker in one or the other branch sending impulses directly through the interventricular septum into the Purkinje network of the contralateral ventricle as well as into that of the homolateral ventricle.

7 There may be a variability from time to time in the degree of auriculoventricular dissociation, indicating that there are other factors involved besides the organic lesions of the bundle branches.

8 In such cases as these, death frequently occurs in an Adams-Stokes attack.

9 More frequent and more careful histopathologic studies of the entire recognizable conduction system are urgently needed because of the uncertainties at present involved in the interpretation of electrocardiographic alterations.

# ERYTHROCYTE FRAGILITY IN PNEUMONIA

ROBERT J NEEDLES, M D

DETROIT

One of the chief causes of death in the valley of the Amazon is lobar pneumonia. This is due in part to the low resistance of the native, a factor which has been discussed in a previous publication<sup>1</sup>. In an industrial enterprise such as the Ford rubber plantation, the control of this disease assumes importance second, perhaps, only to the control of malaria and to general sanitation. In the hospital of the company, located at Boa Vista, Rio Tapajóz, Brazil, there was an admirable opportunity to study tropical pneumonia, and therefore I undertook a series of investigations in an effort to understand the disease more fully.

In the course of the investigations I had occasion to make some tests for the fragility of the erythrocytes. I expected, particularly in cases of jaundice, that the resistance of the red blood cells might become less, but instead in many cases it increased. The results were deemed sufficiently interesting to be reported separately.

A survey of the literature has revealed that little interest has been shown in the study of the fragility of the erythrocytes in cases of pneumonia. The resistance of human red blood corpuscles to hypotonic solutions of sodium chloride has been the subject of considerable investigation in the past. These studies, however, have usually been conducted in instances in which blood dyscrasia, such as hemolytic icterus or purpura haemorrhagica occurred. The test is described in several books on clinical laboratory methods,<sup>2</sup> but in none is any mention made of its usefulness in other than hematologic conditions. One reference to the resistance of the red blood cells in pneumonia was found. Petranyi<sup>3</sup> used such an examination in a series of cases of pneumonia in children. His results, while given in a different scale, parallel ours, that is, in pneumonia he found that the resistance of the erythrocytes to hemolysis was increased.

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1 Needles, R. J. Health Problems in the Amazon Valley, Science **78** 532 (Dec 8) 1933.

2 Todd, J. C. and Sanford, A. H. Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders Company, 1930. Kolmer, J. A., and Boerner, F. Approved Laboratory Technique, New York, D. Appleton & Company, 1931. Stitt, E. R. Practical Bacteriology, Blood Work and Animal Parasitology, Philadelphia, P. Blakiston's Son & Co., 1927. Nicholson, D. Laboratory Medicine, Philadelphia, Lea & Febiger, 1930.

3 Petranyi, Gyoza. Erythrocyte Resistance in Various Stages of Pneumonia, Orvosi hetil **72** 1180, 1928.

The basis for hemolysis of the red blood cells in hypotonic saline solution lies in the osmotic phenomena of such a relationship. The salt concentration of normal blood serum is from 0.8 to 0.9 per cent, and that of the human erythrocyte is about the same strength. When placed in solutions of less concentration than this the corpuscles tend to absorb water from the surrounding fluid medium in an effort to adjust the salt concentration toward an equilibrium. When the amount of salt in the medium is sufficiently low, the erythrocytes absorb so much water that they rupture. This rupture releases hemoglobin into the surrounding fluid, and when this is grossly evident, hemolysis or laking of the blood is said to have taken place.

#### TECHNIC

In most textbooks of laboratory technic directions are given for performing a fragility test. A 0.5 per cent solution of sodium chloride is used, and by adding this standard to graduated amounts of water a series of solutions varying from 0.26 to 0.48 per cent is produced. This method is satisfactory but subject to error.

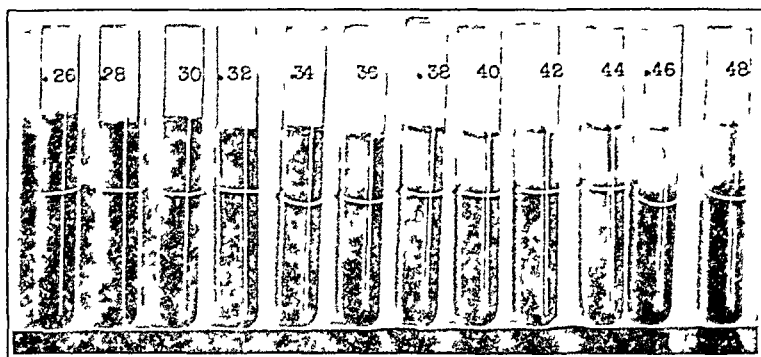


Fig 1—Photograph illustrating the appearance of normal fragility. A faint tinge of beginning hemolysis may be seen at a dilution of 0.44 per cent, which becomes progressively more marked and is complete at 0.36 per cent.

In the tests reported here a series of accurate solutions of sodium chloride have been made by weighing the precise amount of salt necessary on an analytic balance, the solutions being made in volumetric flasks. These standards are made in 1 liter amounts, which is sufficient for many examinations and assures continuously accurate salt concentrations.

In performing the test a set of twelve tubes is made up. These may be of any size, though the convenient Wassermann tube (75 by 15 mm) gives good results. Into each of these is placed from 3 to 4 cc of saline solution, starting with a concentration of 0.26 per cent in the first tube and running up to 0.48 per cent in the twelfth tube, the interval between being 0.02 per cent. The rack of tubes being thus prepared, 2 cc of venous blood is withdrawn from the patient in a clean dry syringe, and 1 drop of blood is quickly placed in each tube. The tubes are then shaken gently, or inverted to insure adequate mixing, and put aside for two or three hours to allow the contents to settle. After this period it is possible to read the results of the test, examining the tubes by transmitted light. The first appearance in a tube of a yellowish or brownish tint in the supernatant fluid is said to mark the point of beginning hemolysis. Normally this

occurs with a concentration of saline solution of from 0.44 to 0.46 per cent. When after a tube is shaken no more sediment can be demonstrated, hemolysis is said to be complete. Normally this occurs with a concentration of 0.36 per cent, and the normal fragility of erythrocytes is from 0.36 to 0.44 per cent (fig. 1).

### OBSERVATIONS

A series of examinations of 100 normal Brazilians of this region, who were of mixed races, including varying percentages of Negro, Indian and white blood, was made. In these persons the fragility of the erythrocytes was found to be from 0.36 to 0.44 per cent, stated in terms of accurately weighed solutions of sodium chloride.

The study embraced a series of 30 cases of typical lobar pneumonia. From these 6 cases were selected for description and graphic representation of temperature and erythrocyte fragility. Cases of different degrees of severity were selected in order to demonstrate the close adherence of the values for fragility to the severity of the illness of the patient.

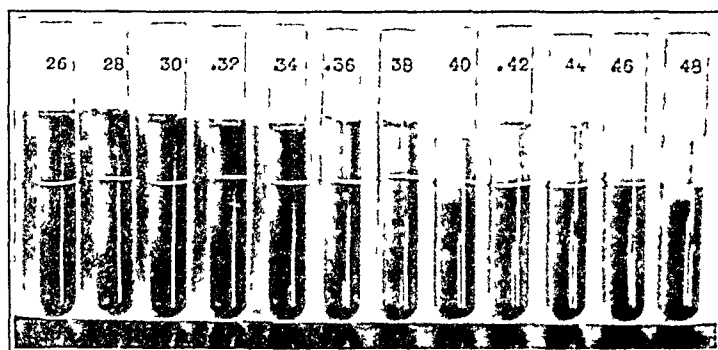


Fig. 2—A fragility test in a case of moderately severe pneumonia. Hemolysis is visible above a concentration of 0.36 per cent, from which point it increases, reaching completion at 0.43 per cent.

From one to four days after the first appearance of lobar pneumonia the resistance of the red blood cells to hemolysis in hypotonic saline solution increases (fig. 2). In mild cases this depression of fragility may not go below 0.4 per cent, while in severe cases it may go as low as 0.32 or 0.3 per cent. The low point of beginning hemolysis persists until from one to three days after the febrile crisis, when a more or less abrupt return to normal occurs. In fatal cases the depression continues with increasing severity to the termination of the disease.

The whole scale of hemolysis is lowered as a unit, i. e., the point at which hemolysis is complete is lowered about the same degree as the point at which hemolysis begins. Therefore, only the latter, as it is easier to read, is considered here. Hence, on the charts fragility is shown as the point at which hemolysis begins and is determined by the first faint yellowish-red discoloration of the supernatant fluid.

CASE 1 (fig 3) —S C C, a Brazilian man aged 38, entered the hospital on the fifth day of illness, demonstrating typical signs and symptoms of lobar pneumonia in the lower lobe of the left lung. He was at no time extremely ill, and after having a temperature between 38 and 39 C (100.4 and 102.2 F) for five days he improved abruptly on the sixth day in the hospital. From this point on his recovery was rapid and uneventful, and he was discharged thirteen days after admission.

This patient had a fragility curve typical of that associated with mild pneumonia. Beginning with figures which were normal or slightly above on the first three days, the curve dropped rather abruptly to 0.4 per cent, at which point it remained until three days after resumption of the normal temperature, when it rose to normal levels and remained there.

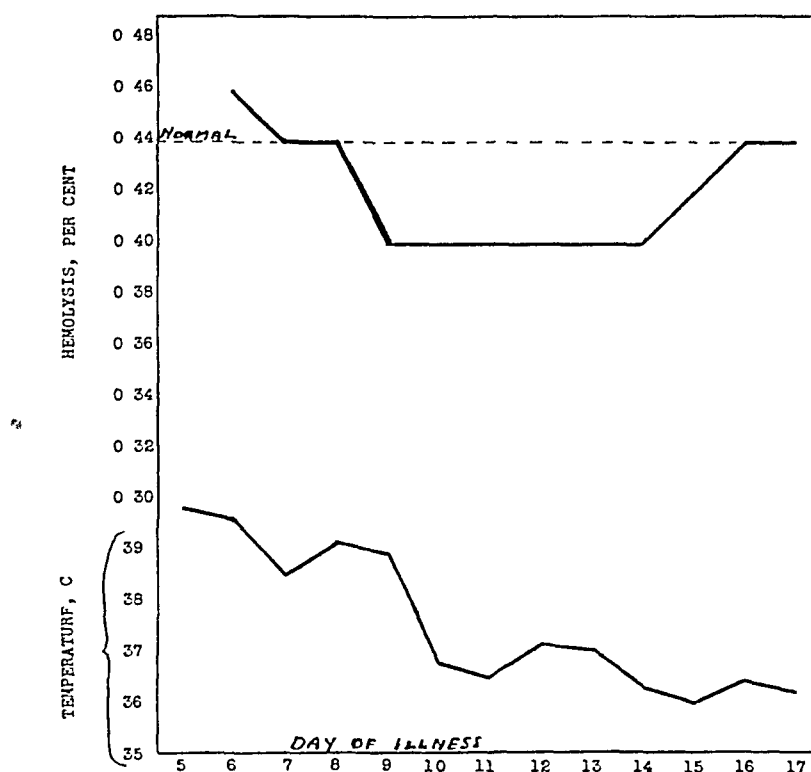


Fig 3 (case 1) —A typical fragility curve in a case of mild pneumonia

CASE 2 (fig 4) —A P de S, a Brazilian man aged 25, entered the hospital on the fourth day of illness with typical signs and symptoms of lobar pneumonia in the lower and middle lobes of the right lung. The course was severe, and the patient for several days was extremely ill, as shown by the temperature chart. The fall in temperature was by lysis, but the recovery was fairly rapid, and the patient was discharged from the hospital thirteen days after admission.

This case illustrates the course of erythrocyte fragility in lobar pneumonia of moderate severity. Starting with subnormal figures on the second day in the hospital, the point of beginning hemolysis dropped steadily and rapidly to as low as 0.36 per cent on the eighth day of the illness. The recovery was not abrupt as shown by the hesitancy with which both the temperature and the erythrocyte fragility returned to normal.

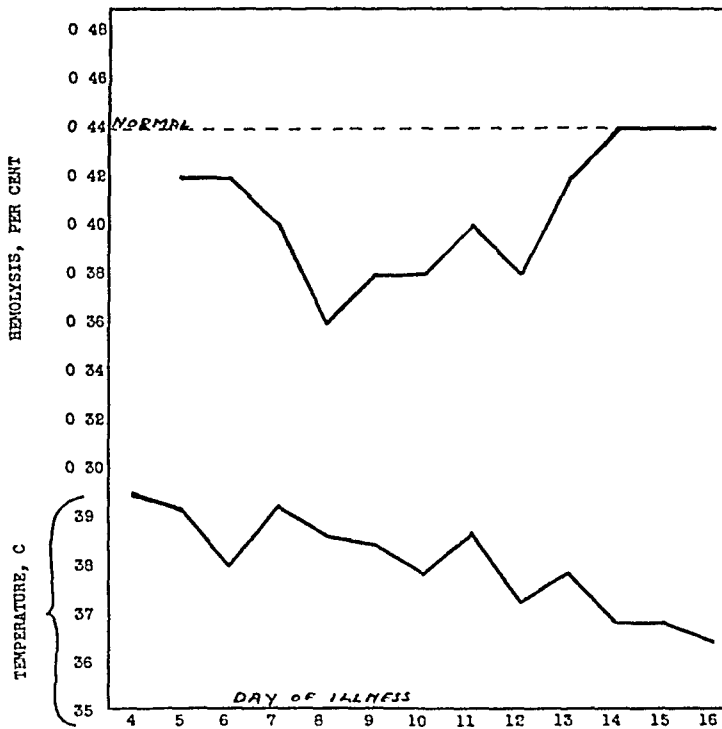


Fig 4 (case 2) —Showing the course of erythrocyte fragility in a case of lobar pneumonia of moderate severity

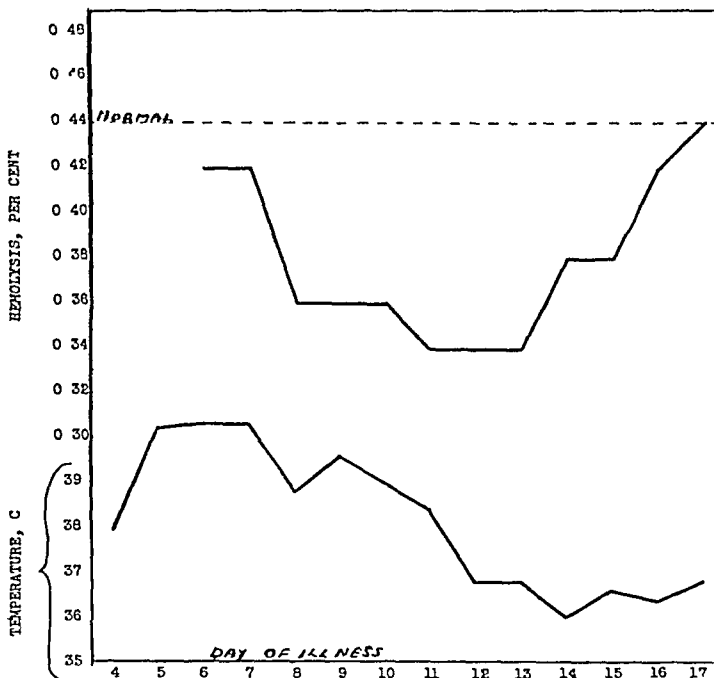


Fig 5 (case 3) —The erythrocyte fragility curve in a case of pneumonia of extreme severity

CASE 3 (fig 5)—J L S, a Brazilian man aged 25 years, entered the hospital on the fourth day of his illness, presenting typical signs and symptoms of lobar pneumonia in the lower lobe of the left lung. He was extremely ill, and for several days little hope was held for his recovery. However, after seven days in the hospital his temperature dropped rather abruptly, and he was discharged as convalescent fourteen days after admission.

The clinical impression of extreme severity was substantiated by the erythrocyte fragility curve. Starting with a subnormal figure on the third day after the patient's admission to the hospital, the point of beginning fragility dropped in one day to 0.36 per cent, paused there for two days and then receded further to the alarming level of 0.34 per cent. The fragility continued at this very low point for three days before returning to normal.

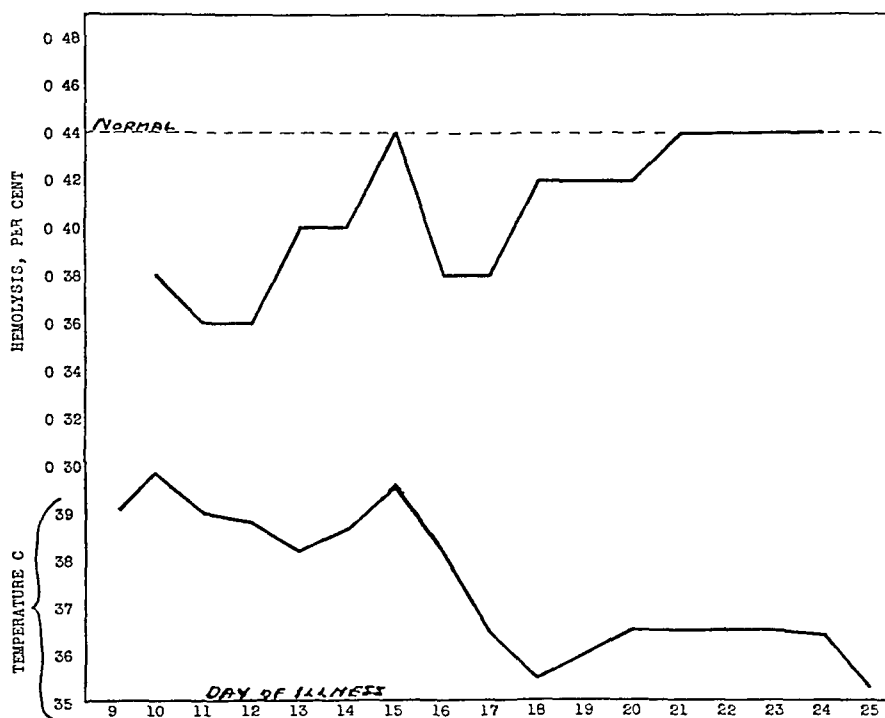


Fig 6 (case 4)—Curves illustrating the erythrocyte fragility in a pneumonic process of a week's duration.

CASE 4 (fig 6)—A F da S, a Brazilian man aged 39 years, entered the hospital on the ninth day of his illness with fully developed lobar pneumonia in the lower lobe of the left lung. His course was extremely severe, and after a temporary lowering of the temperature there were signs of a new involvement in the lower lobe of the right lung, which threatened to prove fatal. The patient rallied, however, and after seventeen days in the hospital was discharged as convalescent.

This case illustrates a primary low figure for erythrocyte fragility, doubtless because the pneumonic process was over a week old at the time of admission. After two days at 0.38 per cent, the hemolysis level rose, and three days later it was at 0.44 per cent, a normal figure. Then it dropped suddenly back to 0.38 per cent, which corresponded well with the clinical impression of new involvement in the lower lobe of the right lung. Following the remission in fever, the fragility figures returned to normal and remained there.



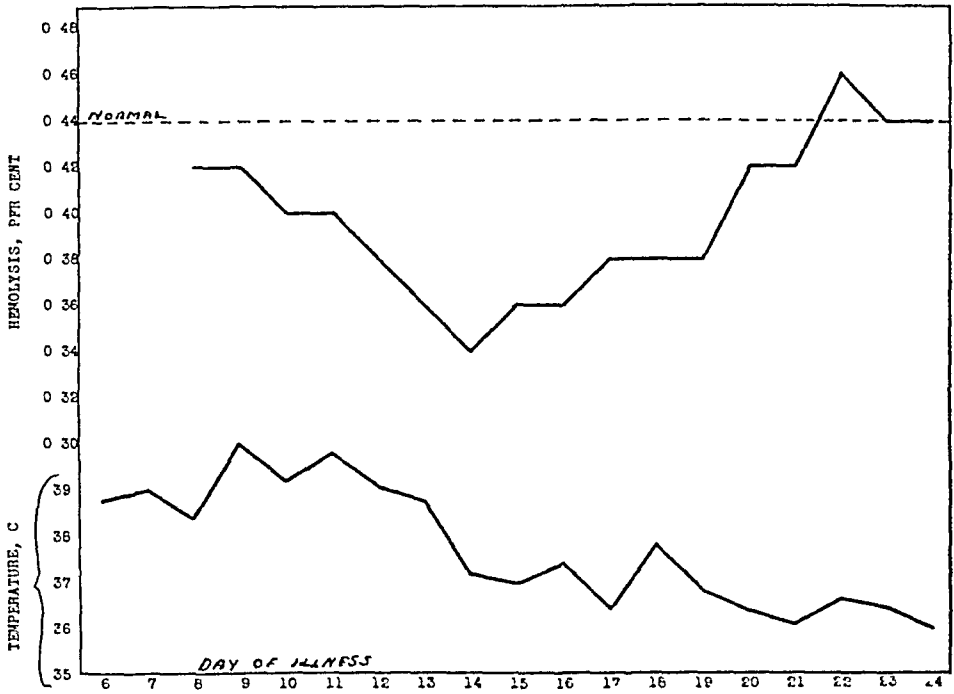


Fig 7 (case 5) —Curves showing the uncertain course of the temperature and the fluctuation at the point of beginning hemolysis

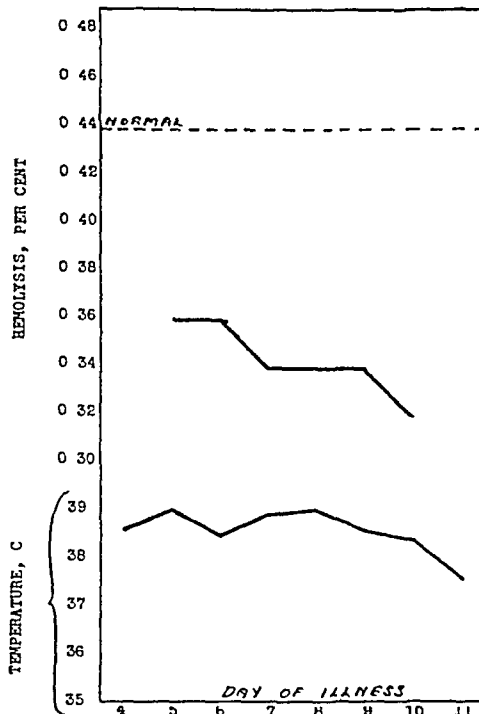


Fig 8 (case 6) —Curves showing progressive depression of the erythrocyte fragility in a fatal case of lobar pneumonia

CASE 5 (fig 7) —B C de M, a Brazilian youth 19 years of age, entered the hospital on the sixth day of his illness. After four days of indeterminate signs and symptoms, on the fifth day he exhibited typical lobar pneumonia in the lower lobe of the left lung. The course was severe and long drawn out, with no abrupt crisis but with several slight recurrences after the initial fall in temperature. The involved area gradually cleared, and the patient was discharged as convalescent after eighteen days in the hospital.

Following the uncertain course of the temperature curve, the point of beginning hemolysis also fluctuated in this case. The low level reached on the eighth day in the hospital and the hesitancy exhibited in returning to normal are in perfect harmony with the signs and symptoms.

CASE 6 (fig 8) —R N de L, a Brazilian man aged 37 years, entered the hospital on the fourth day of his illness with signs and symptoms of lobar pneumonia involving the entire left lung. Treatment was of no avail, and the patient died eleven days after admission. Autopsy showed massive consolidation of both lobes of the left lung, with fibrinopurulent pericarditis.

The first test for fragility of the erythrocytes, made on the second day the patient was in the hospital and on the fifth day of the disease, showed hemolysis beginning at 0.36 per cent. Succeeding daily examinations showed progressive depression of the fragility, and the day before death occurred a low point of 0.32 per cent was reached.

#### COMMENT

I have been unable to show any significant differences in pneumonia as seen in this latitude and that seen in more northern countries. The etiologic agent is the pneumococcus, and apparently any of the four recognized types may act as the infectious agent. Pathologic observations show massive lobar consolidation, such as one sees in pneumonia elsewhere. The sole difference is that owing to the previously debilitated state of many of the patients because of chronic disease and malnutrition pneumonia carries a high mortality rate.

The type of therapy has not seemed to play any part in the changes in fragility. In the first half of the cases studied no specific therapy was used and only supportive treatment was given, but in the latter half the patients were given optochin base. On the latter regimen they fared better. Therefore, as would be expected, when pneumonia is less severe fragility is not depressed to so great a degree.

It is difficult, of course, to say just when in the course of pneumonia the depression in fragility begins to occur. Many of the patients enter late, on the fourth or fifth day of their illness, or even later. These are found to have fragility rates as low as 0.38 or 0.36 per cent on admission. In the few cases which I have been fortunate enough to observe early it seems that the first appearance of decreased fragility, as well as the return to normal figures, lags from one to three days behind the changes in temperature. Thus a patient may enter the hospital with a high fever and maintain that high fever for two or three days before the point of beginning hemolysis begins to drop. Likewise, the depression in fragility may persist for two or three days after the febrile crisis

I have made some study of the relation of other factors, such as the incidence of cultures of the blood giving positive results, the Arneth-Schilling counts, the toxic granulation of neutrophils and the total white blood cell counts, but I have been able to show only that with these special tests patients with severe pneumonia show more marked changes in fragility than those with a mild form of the disease. This relationship, however, needs more detailed study.

#### SUMMARY

Attention is called to the use of a determination of erythrocyte fragility in pneumonia. A modified technic for the carrying out of this test is explained, which gives accurate salt concentrations and uniform results. In pneumonia, depending on the severity of the illness and on its toxicity or the amount of lung tissue involved, the resistance of the red blood cells to hemolysis becomes greater. When the disease is mild, this may amount to as little as from 0.02 to 0.04 per cent, while when it is severe, it may be as great as 0.14 per cent. In fatal cases the resistance of the erythrocytes is very great, becoming progressively more marked as the disease advances.

There is a possible use for such an examination as an aid to prognosis. From the limited number of cases presented it may be stated that mild pneumonia causes only slight changes in fragility. Therefore it may be assumed that as long as the erythrocyte resistance remains above 0.4 per cent the prognosis is good. However, I have seen patients recover in whom the point of beginning hemolysis had been as low as 0.34 per cent. The crisis in fragility lags from one to three days behind the crisis in fever, and it is not unusual to see low fragility readings from one to three days following the restoration of the normal temperature.

The mechanism is not clear. If it were directly dependent on toxicity or on the degree of bacteremia, one would expect the restoration to normal of the fragility of the red cells to be coincident with the cessation of fever. It seems more likely that it is a phenomenon intimately related to the amount of lung tissue consolidated and thus connected with the oxygen-carbon dioxide equilibrium of the blood. Further experimental work is needed to clear these points.

It is acknowledged that the cases reported here all occurred in Brazilians and that there may be some racial idiosyncrasy of which I am not aware. Also, as shown before,<sup>1</sup> most of the patients in this region are carriers of chronic malaria, many have syphilis and almost all have one or more types of intestinal parasites. In nearly all the spleen is enlarged from one to four times. The series of normal patients in which I have shown that the normal limits for erythrocyte fragility in this

area are the same as in more northern climates and in the white race, i e, from 0.36 to 0.44 per cent, would tend to show that the same pathologic reactions would also be present. This is not conclusive and awaits the proof by application of the test in cases of pneumonia in the temperate zone.

Further research should point in two directions, viz, toward infections in general and toward pulmonary disease in particular. I should be greatly interested in the results of the test carried out in a series of cases of pulmonary tuberculosis and of congestive heart failure in which the pulmonary function is seriously impaired.

#### CONCLUSIONS

The fragility of the erythrocytes in pneumonia is discussed, cases are presented, and a modified technic is described. It is believed that the use of the test may open new avenues in the investigation of pneumonia, and it is suggested that the test be employed in cases of other infections, particularly of the pulmonary type. Acknowledgment is made that a difference in climate and race may cause some difference in results. A series of tests for fragility on normal inhabitants of this region is presented.

Dr. Colin Beaton and Dr. Siqueira Mendes granted me permission to use the cases presented, and Senhor Ivahy Ribeiro gave technical assistance.

# Progress in Internal Medicine

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## ALLERGY

A REVIEW OF THE LITERATURE OF 1935

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In January 1935 a review of the current literature on allergy was published in the ARCHIVES OF INTERNAL MEDICINE<sup>1</sup>. The present paper represents a continuation and extension of that work. During the year the number of new titles under the headings anaphylaxis, allergy, asthma, hay fever and eczema has been large, and, as before, a good deal of selection has been necessary and no doubt certain important articles have been missed.

An editorial<sup>2</sup> in *The Journal of the American Medical Association* for June 1, 1935 says "Perhaps it is time now to examine the definition [of allergy] and determine its present status. In the main it would probably be well to restrict the term to those disorders of sudden onset in which a specific tissue hypersensitivity is demonstrable." In last year's review it was pointed out that allergy is used to connote the mechanism of three different states, in each of which there is evidence of tissue sensitiveness. Hay fever and asthma are typical of the group characterized by reactions of the immediate urticarial type whenever the patient comes in contact with the allergen. Certain of the infectious diseases cause a tissue reaction of another kind, namely, an inflammation which appears not in a few minutes but in many hours after contact with the exciting agent. The reaction to tuberculin is the classic example, although one recognizes that its severity, its time relation, and, indeed, its character can be modified by changes in the infected animal as well as in the material and method used for its demonstration. Finally, in certain diseases of the skin there is evidence that the sensitiveness, the allergy, is of the skin alone and not of any other tissue. It is a "local allergy." If all this is true, it is inevitable that the conception of allergy, as previously stated, must apply to a wide variety of clinical states, and, regarded broadly, allergy appears to be intimately concerned

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1 Rackemann, F. M. Allergy. A Review of the Current Literature, Arch Int Med **55** 141 (Jan.) 1935

2 Definition of Allergic Diseases, Editorial, J. A. M. A **104** 2000 (June 1) 1935

with the whole immune process, with the resistance of the host to disease. To my mind this seems proper and wholesome, and I believe that a broad definition is wisest and safest at this time. It is necessary that those who are interested in hay fever, asthma and eczema, that is, in the immediate allergic reaction, should keep an eye on those other clinicians and the bacteriologists who are interested in the late inflammatory allergic reaction. There is definite evidence of a relation between the reactions, and one must understand the principles of both. On the other hand, the group of patients with hay fever, asthma or eczema is so typical and exhibits reactions which are so characteristic that it seems necessary to have a subgroup under the heading of allergy in which to place them. Coca has suggested "atopy," with "atopic" reactions elicited by "atopens," and has included in the definition the factor of heredity. The idea has advantages, even though it would probably be impossible so to define the subgroup that every condition would be placed either squarely in it or squarely out of it. The fact is that with the present knowledge it is impossible to dig beneath the mass of detail to see the fundamental principles under what is called clinical allergy and how far these principles will apply to disease as a whole.

What is the purpose and function of the reactions which are called "allergic"? This question cannot yet be answered, and it is easier to describe a number of possible functions which the reactions do not accomplish. The literature which deals with the relations of allergy and immunity is reviewed well by Lay Martin,<sup>3</sup> who points to an almost complete dissociation of the two conditions, as follows. First, animals once allergic and immune lose their allergy, that is, cutaneous sensitivity, with the passage of time, while retaining their immunity. Second, animals can be immunized without producing allergy at the same time. Third, there is proof that even though cutaneous sensitivity to bacterial proteins may develop in animals, immunity does not develop. Fourth, cutaneous sensitivity can be made to disappear without loss of immunity. Finally, immunity can be transferred passively to other animals without making them allergic, that is, without causing cutaneous sensitivity.

Whereas these statements are all true in a strict sense, a greater consideration of the time factor will modify some of them. For example, as described last year, Kahn has demonstrated that cutaneous sensitivity, abolished promptly by an intravenous dose of antigen, tends to return fairly rapidly after the treatment. Passive immunity is obviously a temporary state dependent primarily on humoral factors.

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3 Martin, Lay. The Recent Trend Toward a Differentiation Between Allergy and Immunity, and the Relationship to Clinical Medicine, *Ann Int Med* 8 483, 1934.

On the other hand, there is increasing evidence that the tissues are the important element in immunity. If allergy is primarily a tissue function while immunity is primarily a humoral function, it is not surprising that the two may be separated under certain circumstances, whereas most of the time they work together.

Kahn lays further stress on tissue reactions in immunity. In two new papers<sup>4</sup> he describes experiments with what might be called double antigens. When diphtheria antitoxic horse serum is mixed with toxin and the mixture is then injected into a normal rabbit, nothing happens, but if it is injected into a rabbit sensitive to horse serum the animal dies because the sensitized tissue attracts and holds the antitoxic horse serum. When the toxin and the antitoxin are injected separately the amount needed to protect a rabbit sensitive to horse serum is definitely greater than the amount needed to protect a normal rabbit. Whether the tissue merely holds the antitoxin in some combination or whether a reaction occurs to destroy the antitoxin is uncertain.

Teale<sup>5</sup> also emphasizes the importance of tissue immunity. In studying the time required for the disappearance of bacteria after injection into the circulation, he noted that the time was about the same in immune animals as it was in normal animals and that the presence or absence of immunity depended not on the primary clearance of bacteria from the blood stream but on a later recurrence of the bacteremia. Experiment showed that in the immune animal a return of bacteremia does not occur even if at that time its blood has no power to protect other animals against the same organism. There is, then, ample evidence to indicate the importance of the tissues, and the interesting point is that tissue reactions can take place regardless of whether or not the blood serum of the animal shows evidence of humoral immunity.

Further light on the development of sensitization comes from the paper by Schultz and Swift.<sup>6</sup> By treating rabbits with repeated intradermal injections of streptococci to produce a low grade cutaneous infection, the authors observed that when the same animals were then sen-

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4 Kahn, Reuben L., and McDermott, E. B. Studies on Tissue Reactions in Immunity. XV. Union Between Specific Antigen and Skin of Protein-Immunized Rabbits, *J. Immunol.* **27** 125, 1934. Kahn, Reuben L. Studies on Tissue Reactions in Immunity. XVI. Capacity of Different Tissues of Protein-Immunized Rabbits to Combine with Antigen, *ibid.* **27** 143, 1934.

5 Teale, F. H. Some Observations on the Relative Importance of the Reticulo-Endothelial Tissues and the Circulating Antibody in Immunity. I. Bacterial Immunity in Relation to the Role Played by the Circulating Antibody and the Tissues Following Intravenous Introduction of the Bacteria, *J. Immunol.* **28** 133, 1935.

6 Schultz, M. P., and Swift, H. F. The Effect of Antecedent Infection and Immunization with Streptococci upon the Reactivity of Rabbits to Horse Serum, *J. Exper. Med.* **60** 323, 1934.

sitized to horse serum the reactions to subsequent doses of horse serum were much more violent than normal. As an explanation of this observation they suggest that the previous treatment with streptococci caused a stimulation of the reticulo-endothelial system and thus acted to improve the antibody-producing mechanism. The previous treatment of the animal had led to a nonspecific change in the response of its antibodies. The thought is interesting in connection with many so-called anamnestic reactions.

In the meantime, Kline and Young,<sup>7</sup> working in M. B. Cohen's clinic, discuss the differences between what they call reversible and irreversible allergic inflammation. They describe the pathologic process which is characteristic of many allergic states. This process consists of edema, with accompanying mononuclear and eosinophilic infiltration, and is seen typically in patients with asthma. This type of inflammation is capable of disappearing without trace. Whether the pathologic process of allergy is a characteristic of a particular agent or of the resistance of the host is an interesting question, hard to answer. An irreversible allergic inflammation is seen in such destructive reactions as the Arthus phenomenon.

#### CHEMISTRY OF HYPERSENSITIVENESS

The chemical nature of the active substance in pollen extracts is still a controversial problem. The standardization of extracts was formerly on the simple but insecure basis of their total nitrogen content. In 1932 Cooke and Stull<sup>8</sup> suggested that the protein nitrogen, the factor precipitable by phosphotungstic acid, is a more accurate index of the strength of the solution and that the active principle is a protein.

Coca,<sup>9</sup> however, took issue with Cooke and Stull. "In a number of consistent experiments, we have seen such a rapid dialysis of phosphotungstic acid-precipitable nitrogen as to make it certain that by far the greatest part of it is not native protein." Furthermore, the contents of the bag after dialysis, while being so low in nitrogen content, retained its skin test activity, the dialysate being quite inert.

In the meantime, Loeb in 1929<sup>10</sup> and 1930<sup>11</sup> demonstrated that the active principle can be inactivated by tryptic digestion and dialysis.

7 Kline, B. S., and Young, A. M. Normergic and Allergic Inflammation. Cases of Reversible and Irreversible Allergic Inflammation, *J. Allergy* **6** 247, 1935.

8 Cooke, R. A., and Stull, A. The Preparation and Standardization of Pollen Extracts for the Treatment of Hay Fever. *J. Allergy* **4** 87, 1933.

9 Coca, A. F. On the Plan of Standardization of Pollen Extracts Proposed by Cooke and Stull, *J. Allergy* **4** 354, 1933.

10 Loeb, L. F. Ueber die chemische Natur der Allergene. III. Pollen von *Alopecurus* (Fuchschwanz Gras), *Klin. Wchnschr.* **8** 926, 1929.

11 Loeb, L. F. Untersuchungen über die chemische Natur des Allergene. *Biochem. Ztschr.* **220** 432, 1930.



and further that it can be precipitated by alcohol. Loeb also concluded that it either is a protein or is closely bound to a protein. In the same year Black<sup>12</sup> noted that the alcoholic precipitate when purified by reprecipitation gave evidences of a carbohydrate and incidentally was skin test-active in a dilution of 1:240,000. In 1932 Gough<sup>13</sup> demonstrated the presence of a carbohydrate in timothy pollen.

It is apparent that the methods and technic involved in this study are of paramount importance. Dialysis is always uncertain, since it depends so much on the membrane used and the time allowed. Indeed, Unger, Cromwell and Moore<sup>14</sup> observed that skin test-active substances are often dialyzable, and in a direct study they could observe no correlation between the response of the sensitive animal and the dialyzable material. Both the dialyzable and the nondialyzable fractions caused a reaction.

These previous studies are reviewed here because another method of analysis has been developed recently. A year ago Spain and Newell<sup>15</sup> devised an apparatus for forcing solution through semipermeable membranes under pressure. The membranes used were no. 300 and no. 1200 cellophane. Such an ultrafilter holds back the colloidal particles, the protein. It was observed that the filtrate was inactive whereas the colloidal residue retained almost all the original activity. The filtrate contained the nonprotein nitrogen, and since it gave a positive reaction to the Molisch test, there is evidence that it contained carbohydrate. On the other hand, the nitrogen precipitable by phosphotungstic acid was not held back completely, and so it must be concluded that the degree of activity is not exactly parallel to that of the precipitable nitrogen.

Meantime, Osgood and Hubbard<sup>16</sup> passed an extract of timothy pollen through several different Seitz filters and observed that the total nitrogen, the nitrogen precipitable by phosphotungstic acid and the nitrogen precipitable by tri-chloroacetic acid were all reduced but that the nitrogen in the fraction precipitable by tri-chloroacetic acid was reduced most of all and that the amount of reduction of this particular nitrogen fraction corresponded closely to the amount of reduction in skin test activity.

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12 Black, J. H. A Soluble Specific Carbohydrate of Ragweed, *J. Allergy* **2** 161, 1931.

13 Gough, G. A Polysaccharide from the Pollen of Timothy Grass, *Biochem. J.* **26** 1291, 1932.

14 Unger, L., Cromwell, H., and Moore, M. Studies on Pollen and Pollen Extracts. VIII. Dialyzability of Pollen Allergens, *J. Allergy* **3** 253, 1932.

15 Spain, W. C., and Newell, J. M. The Ultrafiltration of Ragweed Pollen Extracts, *J. Allergy* **5** 455, 1934.

16 Osgood, Howard, and Hubbard, R. S. The Skin Exciting Activity of a Timothy Pollen Extract As Measured by Its Content of Three Nitrogen Fractions, *J. Allergy* **6** 349, 1935.

Benjamins, van Dishoeck and German,<sup>17</sup> however, state "When pollen extract is filtered through a protein-tight celloidin membrane by means of pressure, positive skin reactions can be obtained with the filtrate in all hay fever subjects" The active substance passing the filter has a small molecular weight This article of Benjamins and his associates, however, contains a more important point If pollen extract was mixed with a colloid (serum is effective, but a variety of other colloids, like egg albumin and gelatin, are equally effective, so the mixture is not an anaphylatoxin), the mixtures caused a strongly positive cutaneous reaction in patients who were insensitive to the pollen extract alone or to the adjuvant alone in the dilutions used Other substances too could activate pollens, certain amino-acids occasionally Tapioca was particularly effective, but other polysaccharides, like starch, inulin and glycogen, had no effect, and dextrin, dextrose and other pure sugars had no effect If the combination of ultrafiltrate and colloid was again filtered there was a great loss of activity in the filtrate, and when the process was repeated a third time with stronger colloid (gelatin) all activity was removed by the filter The results of these experiments suggest that the active principle of pollen extract is in a small molecule which needs a larger complex for its activation

The work of Caulfeild<sup>18</sup> has further complicated the question Working with various chemical fractions of ragweed pollen on a series of cutaneous sites passively sensitized, he observed that desensitization readily followed persistent treatment of the particular site but that desensitization with a fraction did not necessarily leave the site desensitized to the whole extract He concluded that the skin test-active substance in ragweed is not single but multiple and that the reagins are likewise multiple This observation offers another explanation of so many discordant results

Investigations into the production of artificial sensitization to compounds of simple chemical structure have been continued Bernstein<sup>19</sup> sensitized guinea-pigs to the pollen of *Iva xanthifolia* (bur-weed, marsh-elder) by a simple technic He mixed equal volumes of 4 per cent pollen extract and horse serum and let the mixture stand for several days Guinea-pigs were sensitized by three intradermal injections each

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17 Benjamins, C E, van Dishoeck, H A E, and German, J L M Studies on the Active Substance of Grass Pollen I Activation of a Small Molecular Weight Active Group Through Colloidal Substances, *J Allergy* **6** 335, 1935

18 Caulfeild, A H W Prausnitz-Kustner Reaction with Sera of Ragweed Hay Fever Patients to Ragweed Carbohydrate Fractions, *Proc Soc Exper Biol & Med* **31** 573, 1934

19 Bernstein, C, Jr Studies on Anaphylaxis with Pollen, *J Exper Med* **61** 149, 1935

of 0.4 cc at four day intervals. Later when 0.4 cc of the pollen extract was injected intravenously, shock occurred. This is similar to the work of Horsfall,<sup>20</sup> who observed that mixtures of formaldehyde and serum, both native and foreign, will immunize rabbits so that precipitins are formed for homologous and heterologous serums treated with formaldehyde, and at the same time a markedly increased cutaneous sensitiveness develops to formaldehyde alone. Cutaneous tests are made with dilutions from 1:200 to 1:500,000. Later, Horsfall<sup>21</sup> studied a patient sensitive to solution of formaldehyde U.S.P. and observed that any exposure, whether by injection, immersion or (and this is especially interesting) inhalation, produced the characteristic cutaneous manifestations. The hypersensitiveness was strictly specific to formaldehyde. Acetaldehyde, paraldehyde and other aldehydes caused no reaction. Benzaldehyde did cause a reaction, but it was irritating to controls as well. Passive transfer was not accomplished. An interesting observation was the difference in time between reactions to uncombined formaldehyde, which were delayed and reactions to protein treated with formaldehyde, which were immediate. This suggests that the reaction depends on the formation of a substance resulting from the union of formaldehyde with a protein or with a constituent of the skin of the hypersensitive person.

The whole field of sensitization with simple chemical compounds is reviewed by Landsteiner and Jacobs,<sup>22</sup> who report a series of successful experiments in the sensitization of guinea-pigs to a variety of aromatic compounds. These studies, conducted by Spain, Benjamins, Horsfall and Landsteiner, dwell on the theme that specific activity is a function of a small nucleus attached to a larger body having protein characteristics. The picture is familiar in connection with haptens as well as in connection with the carbohydrate complex, which confers species specificity on the protein of the pneumococcus.

Meantime, Ratner and Gruehl<sup>23</sup> sensitized animals to whole milk and observed that shock could be caused by the injection of casein, lactalbumin and lactoglobulin, as well as of a number of treated milks said to be allergen-free. The reduction of antigenic potency by heat depends merely on a partial coagulation which delays absorption by the

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20 Horsfall, Frank L., Jr. Formaldehyde and Serum Proteins, *J Immunol* **27** 553, 1934

21 Horsfall, Frank L., Jr. Formaldehyde Hypersensitiveness. An Experimental Study, *J Immunol* **27** 569, 1934

22 Landsteiner, K., and Jacobs, John. Studies on the Sensitization of Animals with Simple Chemical Compounds, *J Exper Med* **61** 643, 1935

23 Ratner, Bret, and Gruehl, H. L. Anaphylactogenic Properties of Milk. Immunochemistry of the Purified Proteins and Antigenic Changes Resulting from Heat and Acidification, *Am J Dis Child* **49** 287 (Feb.) 1935

digestive tract In another paper <sup>24</sup> Ratner and Gruehl indicate that so-called allergy to carbohydrate foods depends on the small residue of protein which the foods contain and that malt extracts contain hordein and are antigenic while corn syrups and other sugars are non-anaphylactogenic In a third and very useful article Ratner <sup>25</sup> presents the practical aspects of the treatment of milk allergy

In considering chemistry the observations of Cohen <sup>26</sup> on the nature of the house dust allergen must be included Cohen demonstrated that extracts of new and fresh cotton linters cause a reaction very infrequently on the skin of patients sensitive to house dust but that extracts of other cotton which is old and used causes a strong reaction In my own laboratory, the findings in the study of kapok were the same, there is a marked difference in the reactions caused by new and those caused by old kapok These results will be described in a paper by Wagner and Rackemann now in press

#### IMMUNOLOGY OF HYPERSENSITIVENESS

The biologic relationship between substances of similar character is of great practical importance in the clinical management of allergic patients with allergic manifestations There are two methods of studying their relationship

In 1925 Coca and Grove <sup>27</sup> made a study of the atopic reagins and observed that these antibodies could be neutralized When hypersensitive serum containing reagins from a patient with asthma or hay fever was injected into normal cutaneous sites on the arm of normal recipients, the sites became sensitive to the same substances to which the patient was sensitive Coca and Grove observed that if these passively sensitized sites were treated repeatedly with the corresponding allergens injected into the same areas the reactions, which were extensive at first, tended to become smaller later and finally to disappear, the sites were desensitized, but they would show a reaction again when tested further with some other allergen Evidently the desensitization was a highly specific phenomenon In the same article Coca and Grove describe a second method When a mixture of atopic serum (containing reagins to horse dander) and of atopen (the extract of horse dander) was injected into a normal recipient the reagins in the mixture were neutralized, as shown by the fact that a test of the site twenty-four hours later

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24 Ratner, Bret, and Gruehl, H L Anaphylactogenic Properties of Malted Sugars and Corn Syrup, *Am J Dis Child* **49** 307 (Feb) 1935

25 Ratner, Bret The Treatment of Milk Allergy and Its Basic Principles *J A M A* **105** 934 (Sept 21) 1935

26 Cohen, Milton B Observations on the Nature of the House Dust Allergens, *J Allergy* **6** 517, 1935

27 Coca, A F, and Grove, Ella F Studies in Hypersensitiveness XIII A Study of the Atopic Reagins, *J Immunol* **10** 445, 1925

with an extract of horse dander resulted negatively. This second experiment has been repeated by Walzer and Bowman<sup>28</sup> and by Cooke and his associates,<sup>29</sup> and the general principles are confirmed.

These two methods have provided a means of distinguishing between closely related substances in their biologic activity. For example, the horse dander-horse serum relationship has been studied by Tuft,<sup>30</sup> who observed that passively sensitized sites desensitized with horse dander are also desensitized to horse serum, but, on the other hand, horse serum is not capable of desensitizing the sites to horse dander. As Tuft concludes, there is an additional factor in the dander which is not present in the serum. Using the method of desensitization of passively sensitized sites, Simon<sup>31</sup> noted that the serum of patients sensitive to horse serum could sensitize the sites in a normal recipient not only to horse serum but to that of a wide variety of other animals. When later a series of sites were desensitized with guinea-pig serum and then tested with the serums of other animals the reactions were entirely negative. Evidently there is a species-nonspecific factor present in all mammalian serums. The specificity of different species of the Caddis fly has been studied by Osgood<sup>32</sup> with similar methods.

Harley<sup>33</sup> has made a study of reagin-allergen mixtures. He observed that they may produce reactions in normal skin. When the allergen is bound by the reagin in vitro it can be freed by heating to 56 C or enough to destroy the reagin, the union is influenced markedly by time and temperature. To me it seems wiser and safer to use the method by which passively sensitized sites are desensitized with one substance and then tested with another.

Harkavy and Witebsky<sup>34</sup> call attention to the fact that whereas a single serum may contain reagins for a variety of substances, the con-

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28 Walzer, M., and Bowman, K. A Test Tube Neutralization Method for Studying the Identity and Properties of Reagins, *J Allergy* **1** 464, 1930.

29 Stull, A., Cooke, R. A., and Barnard, J. H. The Biologic Identity of Certain Grass Pollens Causing Hay Fever, *J Allergy* **3** 352, 1932. Cooke, R. A., Stull, A., Hebard, S., and Barnard, J. H. Clinical and Serologic Study of the Relationship of Giant (*Ambrosia Trifida*) and Low (*Ambrosia Artemisiaefolia*) Ragweed Pollen, *J Allergy* **6** 311, 1935.

30 Tuft, L. Further Studies in Serum Allergy. VI. Antigenic Relationship Between Horse Dander and Horse Serum Sensitivity, *J Allergy* **6** 25, 1934.

31 Simon, Frank A. Species Non-Specific Antigenic Factor in Mammalian Serum, *J Allergy* **6** 1, 1934.

32 Osgood, Howard. Comparison of Reagins to Separate Species of Caddis Fly, *J Allergy* **5** 367, 1934.

33 Harley, D. Study of Reagin-Allergen Mixtures, *Brit J Exper Path* **14** 171, 1933.

34 Harkavy, J., and Witebsky, E. Studies on Specificity in Multiple Hypersensitiveness by Quantitative Titration and Absorption of Reagins, *J Allergy* **6** 437, 1935.

centration of these reagins may vary to some extent and that in studying reagins it is necessary to consider the dilutions of the serum as well as the dilutions of the allelgic substance

On a somewhat related topic is the paper by Stevens,<sup>35</sup> in which he describes his effort to demonstrate the presence of reagins by chemical means, using those methods which are often successful in demonstrating the combination of agglutinins with bacteria. His results were negative.

#### HOST FACTOR IN ALLERGY

The host factor in allergy has received scant attention of late. Bray<sup>36</sup> discusses the importance of endocrine dysplasias in patients with asthma and hay fever and quotes figures of others to indicate that these disturbances are rare in patients with allergy, just as allergy is a rare complication in patients with frank endocrine disorders. This subject, however, may be more important than it now appears, because in the last analysis there must be some fundamental reason for the fact that certain persons have hay fever and others do not and that tissue reactions of the immediate type are predominant in one case and not in another.

Hara<sup>37</sup> studied hay fever among the Japanese population of Los Angeles and found that the incidence was about 3.5 per cent of the Japanese population in that part of southern California. Evidently the yellow races have no racial immunity.

The complement content of the blood is smaller in persons with allergic disease than in normal persons, as determined by Paul and Pely.<sup>38</sup>

Studies on the relation of the adrenal glands to allergic phenomena have been carried out by Cohen, Rudolph and their associates.<sup>39</sup> Using the quantitative method previously described by Stewart and Rogoff, they sensitized dogs to horse serum and then studied the amount of epinephrine in the blood during the subsequent shock. No significant alteration in the rate of secretion of epinephrine could be demonstrated.

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35 Stevens, F. M. Chemical Study of the Pollen-Sensitizing Antibody Combination, *J. Immunol.* **29** 273, 1935.

36 Bray, G. W. Recent Advances in the Treatment of Asthma and Hay Fever, *Practitioner* **133** 368, 1934.

37 Hara, H. J. Hay Fever Among Japanese. *I. Arch. Otolaryng.* **20** 668 (Nov.) 1934.

38 Paul, B., and Pely, M. Decrease of Complement Content of Blood in Allergic Disease, *Klin. Wchnschr.* **14** 163, 1935.

39 Cohen, M. B., Rudolph, J. A., Wasserman, P., and Rogoff, J. M. The Output of Epinephrine from the Adrenal Glands During Anaphylactic Shock, *Am. J. Physiol.* **106** 414, 1933.

Cohen and Rudolph<sup>40</sup> experimented on man by giving large doses of strychnine, in the hope that this would stimulate the secretion of epinephrine. Doses up to  $\frac{1}{6}$  grain (0.01 Gm) were injected intramuscularly, producing hypertonicity in most of the patients. The asthma was partially relieved, but the good effect was overshadowed by the complicating hypertonicity, and consequently the method can have no general use.

In another series of studies Cohen and Rudolph<sup>41</sup> investigated the possible therapeutic effect of extract of the adrenal cortex. A material called "interrenalin," made by Dr. Rogoff and found potent in patients with Addison's disease, was administered for several weeks to 4 patients with severe asthma. No effect, however, was observed. On the other hand, Wolfram and Swemer<sup>42</sup> studied the effect of extract of the adrenal cortex in protecting guinea-pigs against anaphylactic shock and noted that the majority of animals survived if the extract was administered from two to six hours before the test dose.

None of these studies are critical, but they indicate that there is no evidence that hay fever and asthma depend on a definite alteration in the endocrine, and particularly in the adrenal, function of the patient.

#### DIAGNOSIS

*Discrepancy Between Cutaneous Reactions and Symptoms*—This has received further attention, and little by little students of allergy begin to realize that skin tests are far from giving the answer to every problem. This point was made last year, but repetition can do no harm.

Colmes, Guild and Rackemann<sup>43</sup> made cutaneous tests on the employees of a large bakery. Of 32 men, 15 gave a positive reaction to one or other allergen, but of these only 1 had symptoms which could be attributed to sensitiveness to wheat. For cutaneous sensitivity to develop is common, but for clinical sensitiveness to develop some additional factor, some "activator," is required.

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40 Cohen, M. B., and Rudolph, J. A. Studies on the Relation of the Adrenal Glands to Allergic Phenomena. II. The Therapeutic Effect of Strychnine Stimulation of the Adrenal Medulla in Asthma, *J. Allergy* 6: 404, 1935.

41 Cohen, M. B., and Rudolph, J. A. Studies on the Relation of the Adrenal Glands to Allergic Phenomena. III. On the Specific Therapeutic Effects of Cortical Adrenal Extract in Asthma, *J. Allergy* 6: 279, 1935.

42 Wolfram, J., and Swemer, R. L. Cortin Protection Against Anaphylactic Shock in Guinea Pigs, *J. Exper. Med.* 61: 9, 1935.

43 Colmes, A., Guild, B. T., and Rackemann, F. M. Studies in Sensitization. The Influence of Occupation on Human Sensitization as Determined in a Study of Thirty-Two Bakers, *J. Allergy* 6: 539, 1935.

At the end of 1934, Rowe<sup>44</sup> submitted an evaluation of cutaneous reactions in patients sensitive to food and demonstrated, first, that the method of making cutaneous tests is of great importance and, second, that the substance used for the test is also of great importance, that two extracts bearing the same label often give widely different results. His observations show that in certain cases a positive reaction has no clinical significance, while in other cases the patient might be truly sensitive and yet fail to give a cutaneous reaction. Other observers have come to a similar conclusion from their clinical experience.

Colmes,<sup>45</sup> for example, observed that in 250 patients with asthma the cutaneous reactions were clinically important in only 40 per cent. He studied 222 patients with perennial vasomotor rhinitis and observed that the reactions were of importance in 25 per cent. He followed 93 patients with urticaria and noted that the reactions were significant in only 4 per cent. In patients with hay fever, however, the results were satisfactory, for in practically every instance the reactions and the symptoms seemed to go together.

Part of this discrepancy depends, of course, on the fact that the cutaneous reaction persists long after clinical sensitiveness has disappeared. Thus, Spink and Augustine<sup>46</sup> observed that extracts of *Trichinella* which produce immediate reactions in patients with trichinosis cause an immediate positive cutaneous reaction long after the disease has subsided. The reaction for precipitin likewise persists for a time after symptoms have cleared, but it does not last so long as the cutaneous sensitivity.

*The Leukopenic Index*—Vaughan<sup>47</sup> has continued his studies, observing that a fall of the total number of leukocytes during digestion of a food to which the patient is sensitive corresponds to the symptoms in 81 per cent of the cases. It is his experience that cutaneous reactions correspond in only 64 per cent of the cases. Vaughan noted that the best time to demonstrate the fall in the leukocyte count is from thirty to ninety minutes after ingestion of the food. Mathematically the index is an expression of the amount of decrease in terms of the initial leukocyte count. Rinkel<sup>48</sup> has confirmed Vaughan's observations,

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44 Rowe, Albert, H. An Evaluation of Skin Reactions in Food Sensitive Patients, *J Allergy* **5** 135, 1934.

45 Colmes, A. A Clinical Evaluation of the Positive Skin Reaction in Asthma, Urticaria, Vasomotor Rhinitis and Seasonal Hay Fever, *New England J Med* **212** 725, 1935.

46 Spink, W. W., and Augustine, D. L. The Diagnosis of Trichinosis with Especial Reference to Skin and Precipitin Tests, *J A M A* **104** 1801 (May 18) 1935.

47 Vaughan, W. T. Further Studies on Leukopenic Index in Food Allergy, *J Allergy* **6** 78, 1934.

48 Rinkel, H. J. The Leucopenic Index in Allergic Diseases, read before the Association for the Study of Allergy, June 1935.



stating that the index is an important diagnostic aid, especially in the detection of sensitivity to a food. In Rinkel's experience one count forty minutes after the ingestion of food is satisfactory in 80 per cent of the cases.

*Eosinophilia*—This is always a striking characteristic of allergy, being present in all the different manifestations. A rapid method for its determination is described by Friedman,<sup>49</sup> who recommends the use of a white blood cell pipet for making the count but with a diluting fluid containing 5 per cent each of an aqueous solution of eosin and of acetone in 100 cc of water to be substituted for the usual dilute acetic acid. With this staining fluid the eosinophil cells are easily detected, and the other leukocytes can be seen at the same time. I have tried this method and can say that it is good.

Spangler<sup>50</sup> studied the eosinophil count in persons with syphilis and points out that the number of persons showing eosinophilia is greater if a larger number of counts is made. Evidently the proportion of eosinophils varies from time to time and within fairly wide limits.

The importance of eosinophils in the sputum of patients with asthma is emphasized by Knott and Pearson,<sup>51</sup> who state that the number of eosinophils tends to decrease as secondary infections appear. This subject needs further study, because personal experience indicates that high figures for the eosinophil count in the blood are often noted in cases of a chronic severe type of asthma, including those in which a search for possible causes in foods and dusts is mostly without result. In 1 or 2 cases it has seemed as though the height of the eosinophil count occurred when the severity of the asthma was greatest. That eosinophilia may persist for several years after recovery is the point of a paper by Theiler, Augustine and Spink,<sup>52</sup> who followed 7 cases of trichinosis for more than five years after the attack and observed that in 3 there was still eosinophilia of over 5 per cent.

*The Clinical History*—This remains the one most important factor in the diagnosis of the exciting cause of asthma. This fact was emphasized in the review of last year, and it deserves emphasis again.

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49 Friedman, Townsend B. A Rapid Method for the Determination of Blood Eosinophilia, *J A M A* **103** 1618 (Nov 24) 1934.

50 Spangler, R H. Eosinophilia in Syphilis, *J Lab & Clin Med* **20** 733, 1935.

51 Knott, F A, and Pearson, R S B. Eosinophilia in Allergic Conditions, *Guy's Hosp Rep* **85** 94, 1935.

52 Theiler, H, Augustine, D L, and Spink, W W. On the Persistence of Eosinophilia and on Immune Reactions in Human Trichinosis Several Years After Recovery, *Parasitology* **27** 345, 1935.

## CLINICAL MANIFESTATIONS

*Hay Fever* —Pollen in the Atmosphere Studies of atmospheric pollen have been continued Durham<sup>53</sup> describes a gyrating instrument which can be rotated with a handle so as to draw in a large volume of air and collect on a glass slide the pollen which it contains Nineteen hundred revolutions are equivalent to a twenty-four exposure, so that the machine makes it possible to test the concentration of pollen at any point in a few minutes With this machine and by other methods Durham has gathered useful data, presented in two papers,<sup>54</sup> on the pollen in various areas in North America

Vaughan and Crockett<sup>55</sup> discuss the importance of goldenrod and in another paper with Graham<sup>56</sup> compare the different surveys of pollen in Virginia which have been made in the last six years

Sellers<sup>57</sup> describes the relative importance of grasses, weeds and trees in Texas

Surveys of the concentration of pollen are coming in from foreign countries From Scandinavia comes a survey by Baagøe,<sup>58</sup> and from Havana, one by Alvarez<sup>59</sup> From Australia, Sharwood<sup>60</sup> describes the pollen content of the Melbourne air during the hay fever season from August 1933 to March 1934 From Hungary comes the report by Hlaváček and Blatný<sup>61</sup>

Molds in the air as a source of hay fever and asthma are receiving more attention Prince, Selle and Morrow<sup>62</sup> describe the cultures obtained by exposing Sabouraud plates to the air under different cir-

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53 Durham, O C A Simple Apparatus for Determining the Pollen Content of the Air, *Aerologist* **11** 10, 1935

54 Durham, O C The Pollen Content of the Air in North America, *J Allergy* **6** 128, 1935, Pollen Studies in Selected Areas, *J A M A* **104** 1486, (April 27) 1935

55 Vaughan, Warren T, and Crockett, R W An Assay of Goldenrod as a Cause of Hay Fever, *Ann Int Med* **6** 789, 1932

56 Vaughan, Warren, T, Graham, W R, and Crockett, R W Hay Fever Pollen Prevalences in Virginia Review of a Six Year Survey, *Virginia M Monthly* **60** 158 (June) 1933

57 Sellers, Erle D Pollinosis in the Southwest, *South M J* **28** 710, 1935

58 Baagøe, K Pollen Content of Air in Hay Fever Season, *Ugesk f læger* **96** 570, 1934

59 Alvarez, J Cadrecha Pollen in Air of Havana, *Rev med cubana* **45**. 651, 1934

60 Sharwood, Marjorie M The Pollen Content of the Melbourne Air During the Hay Fever Season of August 1933 to March 1934, *M J Australia* **1** 326 (March 16) 1935

61 Hlaváček, V, and Blatný, C The Quantity of Pollen in Atmosphere of Prague and Its Relation to Atmospheric Changes, *Casop lék česk* **73** 1021, 1934

62 Prince, H E, Selle, W A, and Morrow, M B Mold in Etiology of Asthma and Hay Fever, *Texas State J Med* **30** 340, 1934

cumstances and the check of the results on their patients by testing them with extracts of corresponding molds. Of 18 patients tested, 11 showed positive cutaneous reactions to mold, and in 7 of the 11 the treatment "is encouraging."

The subject of molds as a whole is reviewed in an excellent article by Feinberg,<sup>63</sup> who includes a good bibliography. Positive reactions to molds and yeasts were obtained in 47 of 123 patients with hay fever and asthma, and, more important, it was possible to demonstrate that in many cases these molds were the actual cause of the difficulty.

A helpful botanic review of the fungi is that by Downing and Cousins,<sup>64</sup> who describe the exhibit of fungi at the meeting of the Massachusetts Medical Society. The generic relationship of the thallus plants, including algae and fungi, the mosses, the ferns and the seed plants, are described simply and clearly.

The specific treatment of hay fever is receiving rather less attention so far as the technical details are concerned. Cooke and his co-workers<sup>65</sup> describe the results of transfusion of blood to new patients, using the blood from other patients who appeared to be doing well. As much as 500 cc of blood was given at a time, and the results were satisfactory in 80 per cent of the cases. Another series of patients received subcutaneous doses of 10 cc each of blood from successfully treated patients, and again the results were fairly good, with a satisfactory outcome in 60 per cent of the cases. The interesting part of this study was the comparison of the serum reagins, for no material difference in the sensitizing capacity of the patient's blood was noted before or after the treatment by transfusion. From this Cooke concludes that the protection afforded by transfusion does not depend on the overproduction of antibodies. In another part of the work, the same authors report that although ragweed pollen extract can neutralize *in vivo* the reagins in the serum of sensitive but untreated patients, it does not neutralize the reagins in the serum of patients who have been treated successfully with it. After treatment the serum-ragweed mixture is quite capable of passively sensitizing the cutaneous sites in normal persons. The authors conclude that successful treatment results in the development of an immune body which prevents the union of antigen and antibody.

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63 Feinberg, Samuel M. Mold Allergy. Its Importance in Asthma and Hay Fever, Wisconsin M. J. **34** 254, 1935.

64 Downing, J. G., and Cousins, S. M. Exhibit of Fungi Pathogenic to Man Shown at the One Hundred and Fifty-Third Anniversary of the Massachusetts Medical Society, New England J. Med. **211** 963, 1934.

65 Cooke, R. A., Barnard, J. H., Hebard, S., and Stull, A. The Mechanism of Protection Produced by Injection of Pollen Extract in Hay Fever Patients, J. Allergy **6** 593, 1935.

\* Last year the report of Lichtenstein <sup>66</sup> on intravenous pollen therapy was described. No one has reported on the use of the method since.

Brown <sup>67</sup> continues to treat his patients with maximum doses of pollen extracts, reaching in many cases a dose of 1 cc of a 1:10 dilution, which represents a content of from 100,000 to 200,000 units. With this treatment the cutaneous reaction disappears almost entirely, and all of his patients have done well.

Permanent results following the treatment for late hay fever are reported by Vander Veer and Clarke <sup>68</sup> in a group of 159 patients. Twenty per cent were cured, 33 per cent were greatly improved, 13 per cent were decidedly improved, and in 34 per cent this condition was as bad as ever as soon as the annual or perennial treatment was stopped.

Obviously, the problem of hay fever is not solved.

*Asthma*—"De asthmate antiquo" is the title of a short paper by Baumann <sup>69</sup> in which he reviews the history of asthma in antiquity. The Greeks had three classifications of difficult breathing: dyspnea, asthma and orthopnea. The article is worth reading.

The pathology of the vessels of the pulmonary circulation is well described in an important study by Brenner, <sup>70</sup> of Queen's Hospital, Birmingham, England.

Bubert and Warner, <sup>71</sup> as well as Michael and Rowe, <sup>72</sup> described the pathologic changes in patients who died of asthma.

Cutler and Wood <sup>73</sup> have developed a new method for producing experimental endobronchial occlusion. The injection of a 25 per cent aqueous solution of acriflavine hydrochloride will produce aseptic necrosis of the mucosa, which leads later to proliferation and fibrosis. Collapse occurs only in case all the bronchi to a certain lobe are occluded. The occurrence of collapse in patients with asthma has been

66 Lichtenstein, M. R. Intravenous Pollen Therapy, *J. Allergy* **5** 230, 1934.

67 Brown, G. T. Further Experiences with Maximum Dosage Pollen Therapy, *J. Allergy* **6** 86, 1934.

68 Vander Veer, A., and Clarke, J. A., Jr. Permanent Results Following Treatment for Late Hay Fever, *J. Allergy* **6** 551, 1935.

69 Baumann, E. D. De asthmate antiquo, *Janus* **38** 139, 1934.

70 Brenner, O. Pathology of the Vessels of the Pulmonary Circulation. *I Arch. Int. Med.* **56** 211 (Aug.) 1935, *II* **56** 457 (Sept.) 1935, *III* **56** 724 (Oct.) 1935, *IV* **56** 976 (Nov.) 1935, *V* **56** 1189 (Dec.) 1935.

71 Bubert, H. M., and Warner, C. G. Fatal Asthma. Report of a Case with Bronchial Measurements, *J. A. M. A.* **104** 1469 (April 27) 1935.

72 Michael, P. P., and Rowe, A. H. Pathology of Two Fatal Cases of Bronchial Asthma, *J. Allergy* **6** 150, 1935.

73 Cutler, E. C., and Wood, C. B. Studies on Endobronchial Occlusion, *Surg., Gynec. & Obst.* **59** 501, 1934.

stressed by Waldbott and Snell<sup>74</sup> In my experience the collapse of one lobe has occurred in 2 cases It is surprising that it does not occur more often, since the immediate pathologic change seems to be the formation of unusually sticky and tenacious exudate If this exudate can cause partial occlusion, why not complete occlusion?

Studies of the total pulmonary capacity and its subdivisions in patients with emphysema, asthma and pulmonary fibrosis are presented by Kaltreider and his associates<sup>75</sup> in a series of excellent articles Stress is laid on the ratio between the amount of residual air and the total capacity

Changes in ventilation as influenced by changes in altitude are discussed by Wittkower and Wolfer,<sup>76</sup> who point out that at high altitudes the complemental air falls and the patient feels better On the other hand, the vital capacity is also lowered

Treatment Treatment has been advanced in several minor ways but without radical change in the general method The inhalation of epinephrine is the newest procedure Graeser and Rowe<sup>77</sup> report that when a special 1:100 extract of epinephrine is used in a special atomizer many slight attacks can be relieved My experience corroborates the observation, and the method appears to be useful On the other hand, when patients use the spray more or less constantly one wonders what may be the ultimate effect of such continuous contraction on the bronchial mucous membrane

The effect of viosterol on hay fever and asthma has been studied by Rappaport and his associates,<sup>78</sup> who observed that viosterol is an effective adjuvant to the ordinary pollen treatment Others have used cod liver oil, and there seems little doubt that the increase of vitamins has a beneficial effect I agree to this and observe that my patients with severe asthma often begin to improve greatly as soon as they reach the point where they can take an adequate amount of a well rounded diet The

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74 Waldbott, George L Allergic Death VII Protracted Shock, *Arch Int Med* **54** 597 (Oct) 1934 Waldbott, George L, and Snell, A D Pulmonary Lesions Resembling Pneumonia as the Result of Allergic Shock, *J Pediat* **6** 229, 1924

75 Kaltreider, N L, Hurtado, A, and Brooks, W D W Studies on Total Pulmonary Capacity and Its Subdivisions, *J Clin Investigation* **13** 1027 and 1053, 1934, **14** 81 and 94, 1935

76 Wittkower, E, and Wolfer, R Ueber den Atmungsmechanismus und-mechanismus der Asthmatiker in Hohenklma und bei Ubergang in verschiedene Hohen, *Wien Arch f inn Med* **26** 241, 1935

77 Graeser, J B, and Rowe, A H Inhalation of Epinephrine for the Relief of Asthmatic Symptoms, *J Allergy* **6** 415, 1935

78 Rappaport, B Z, Reed, C I, Hathaway, M L, and Struck, H C Treatment of Hay Fever and Asthma with Viosterol of High Potency, *J Allergy* **5** 541, 1934

state of the nutrition is important in overcoming chronic infections of every kind

New varieties of treatment by inoculation have been suggested Maddox and Back <sup>79</sup> recommend autohemotherapy, with five doses at weekly intervals, each of 10 cc of blood drawn and reinjected immediately Their results were good Johnston <sup>80</sup> uses the patient's urine, "after thorough filtration" and with the addition of a preservative, giving doses every three or four days until a total of 9 cc has been injected

In the treatment of rheumatism Cecil and his associates <sup>81</sup> recommend malarial therapy, which was first used by Wagner-Jauregg in 1917 on patients with dementia paralytica Their patients with rheumatoid arthritis showed good results but had a relapse later The method should be borne in mind as possible treatment in intractable cases of asthma

Vaccines administered by mouth have been reintroduced of late Rockwell, Van Kirk and Powell <sup>82</sup> quote Besredka as saying that the oral administration of vaccine has been successful in cases of typhoid The authors prepared capsules containing dry organisms, 100 billion each of a rough strain of *Pneumococcus* type I and a mouse-virulent laboratory strain of hemolytic *Streptococcus* One capsule was given every day for a week and then one capsule per week The capsules were given to 462 persons, and in this group the incidence of colds decreased by 57 per cent of the previous experience, whereas in the control group observed at the same time the incidence of colds during that particular winter decreased 12 per cent of the customary number Oral desensitization to common foods has been described before, but Keston, Waters and Hopkins <sup>83</sup> report their experiences

Postural drainage as a treatment of persons with asthma is urged by Shambaugh and Alter, <sup>84</sup> especially for those who have thick, viscid bronchial exudate Morning and night the patient kneels on a chair, places his hands on the floor and tries to clear the tubes by coughing In 50 cases the results were good, so good that some of the patients have been free from asthma for four years since the treatment was stopped

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79 Maddox, K, and Back, R Autohemotherapy in the Treatment of Bronchial Asthma, *M J Australia* **1** 277, 1935

80 Johnston, H A Autodesensitization of Allergic Conditions, *California & West Med* **41** 289, 1934

81 Cecil, R L, Friess, C, Nicholls, E E, and Thomas, W K S Malarial Therapy in Rheumatoid Arthritis, *J A M A* **105** 1161 (Oct 12) 1935

82 Rockwell, G E, Van Kirk, H C, and Powell, H M Oral Immunization to Colds, *J Immunol* **28** 475, 1935

83 Keston, B M, Waters, Irene and Hopkins, J Gardner Oral Desensitization to Common Foods, *J Allergy* **6** 431, 1935

84 Shambaugh, N F, and Alter, S M Control of Bronchial Asthma, *Science* **81** 210, 1935

The injection of iodized oil into the trachea is advocated by Balyeat and his associates,<sup>85</sup> who point out that the high gravity of the oil forces the bronchial plugs upward and replaces pockets of pus with a nonirritating, nontoxic substance. The results were good in 35 and poor in only 5 cases.

Helium, discovered for medicinal use by Barach,<sup>86</sup> may prove to be a life-saving measure. Helium has an atomic weight of 4 and a density of 0.138. When it is substituted for the nitrogen in the air the mixture is 66 per cent lighter. The light weight and the small density of helium make it possible to force mixtures of helium and oxygen through a small hole in 50 per cent larger quantity than mixtures of nitrogen and oxygen. Helium itself is nontoxic. One difficulty is that the gas is so light and so penetrating that a special form of tent is required for its use.

Somewhat related to the treatment of allergy is an interesting report of the therapeutic use of localized allergy by Garvin and Frumess.<sup>87</sup> A boy of 11 had a bad ulcer of the leg, the authors injected into the surface of the ulcer some potent egg-sensitive serum and the next morning had the boy eat three eggs on an empty stomach. A violent local reaction took place, after which the ulcer began to heal, and in seventeen days the healing was complete.

Epinephrine injected subcutaneously is now, as always, the principal standby. Several of my patients who have taken epinephrine in large quantities and in frequent doses have been noted to have albuminuria, and in one or two instances edema of the ankles was noted also. So far, no formal study has been made of this observation, but it is well to recall the work of Starr,<sup>88</sup> who observed that when the blood supply of the kidney was impeded in rabbits, albuminuria followed. Apparently renal vasoconstriction, which might cause an increase in the normal, intermittent interruption of the glomerular circulation, can result in a disturbance of the glomerular endothelium.

#### THE NOSE AND THROAT IN ALLERGY

The Warwick<sup>89</sup> method of treatment of hay fever and vasomotor rhinitis is an innovation which has enjoyed a good deal of exploitation.

85 Balyeat, R. M., Seyler, L. E., and Shoemaker, H. A. The Diagnostic and Therapeutic Value of the Intratracheal Use of Iodized Oil in Cases of Intractable Asthma, *Radiology* **24** 303, 1935.

86 Barach, Alvan L. Use of Helium as a New Therapeutic Gas, *Proc. Soc. Exper. Biol. & Med.* **32** 462, 1934.

87 Garvin, P. D., and Frumess, G. M. The Therapeutic Use of Localized Allergy, *J. A. M. A.* **104** 2333 (June 29) 1935.

88 Starr, I., Jr. The Production of Albuminuria by Renal Vasoconstriction in Animals and Man, *J. Exper. Med.* **43** 31, 1926.

89 Warwick, H. L. Desensitization (Ionization) of Nasal Mucous Membranes for Relief of Asthma, *Texas State J. Med.* **30** 210, 1934.

By using a solution of electrolytes with the sulfates of zinc, tin and cadmium and an alloy of the same minerals as an electrode, it has been possible to attract electrically the positive metallic ion to the negative pole in the submucosal tissues of the nose. This treatment is now widely used and with a good deal of success, certainly at first. It is too early, however, to know of the end-results. Tobey<sup>90</sup> has used it on 16 patients. Eight had hay fever and obtained 85 per cent relief. Eight had hyperesthetic rhinitis, and 3 of them had asthma as well, in 1, the Warwick method of treatment resulted in complete relief from the asthma for a period of six months, while in 2 others 50 per cent relief lasted for two months and six months, respectively. The two Alexanders<sup>91</sup> watched 25 patients with seasonal or perennial "hay fever" before and after the Warwick treatment and observed that 11 obtained complete and 5 partial relief. The concentration of reagents in the blood was the same before and after treatment and regardless of the result. Evidently the immediate results of the treatment are fairly good. So far, the chief objections are, first, that the machine, the solutions and the electrodes are expensive and, second, that the local reactions which occur at once may last up to forty-eight hours and be of considerable severity.

Meantime, Walsh and Lindsay<sup>92</sup> have made further studies of nasal polyps and state that they can be divided into two types, according to the predominance of eosinophils. Surgical intervention in cases of the different types gives different results, in patients who had polyps with few or no eosinophils the result was distinctly satisfactory, while in other patients whose polyps contained many eosinophils the results were disappointing. A year ago Kern and Schenck<sup>93</sup> concluded that the finding of mucous polyps in the nose warranted the assumption that the patient was of allergic strain. My experience coincides with this in the main, but there are exceptions, and it seems possible that Walsh and Lindsay have offered an explanation of these exceptions. If polyps are present without eosinophils, it may be that polyps do not necessarily and always depend on the repeated insults of some extrinsic factor to which the patient is hypersensitive.

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90 Tobey, H. G. Experiences in Ionization of the Nasal Mucous Membrane, *New England J. Med.* **213** 230, 1935.

91 Alexander, H. L., and Alexander, J. H. Ionization of the Nasal Mucosa Relationship Between Reagents in the Blood and the Effect of Treatment, *J. Allergy* **6** 240, 1935.

92 Walsh, T. E., and Lindsay, J. R. Cytology, of Nasal Polyps, *Arch. Otolaryng.* **20** 649 (Nov.) 1934.

93 Kern, R. A., and Schenck, H. P. Allergy a Constant Factor in the Etiology of So-Called Mucous Nasal Polyps, *J. Allergy* **4** 485, 1933.



## DRUG ALLERGY

In a special article written for *The Journal of the American Medical Association* Kracke and Parker<sup>94</sup> describe the relationship of drug therapy to agranulocytosis. The bibliography is excellent and useful. About the same time, there appeared an article by Hunter<sup>95</sup> entitled "Agranulocytosis—Drug or Protein Allergy As a Cause of Agranulocytosis and Certain Types of Purpura." Hunter has also reviewed the literature and has done it completely, so that his work will be the basis for other articles on the subject for some time. According to Hunter, agranulocytosis was first described by Schultz<sup>96</sup> in 1922. This was twelve years before Madison and Squier<sup>97</sup> published their first paper in October 1933 and thus did so much to develop the whole field of drug allergy. In reviewing the immense amount of material Hunter points out that in most cases the symptoms of agranulocytosis follow the second course of treatment with a particular drug. The patient has taken this drug before and then allows an interval of time to elapse before taking it again. It is the second dose which causes the difficulty. If always true, the fact is important, because it alone is strong support of the opinion that agranulocytosis is the result of allergic reaction. A case in point is that described by Walter<sup>98</sup>. Hexylresorcinol was applied persistently to the skin over a period of five months, and then came a period without further use of the drug. Twenty-six months later a severe dermatitis resulted from a single brief contact with hexylresorcinol. Meantime, it is interesting to compare Vaughan's observations on the leukopenic index described previously with this other new knowledge. Herz<sup>99</sup> points out that the difference in the ability of various drugs to cause agranulocytosis depends on their different chemical structure, regardless of whether the hydrogen atom is replaced by another radical. In aminopyrine, for example, the NH radical is replaced by a benzene ring, and the product is frequently the cause of

94 Kracke, R. R., and Parker, F. P. The Relationship of Drug Therapy to Agranulocytosis, *J. A. M. A.* **105** 960 (Sept. 21) 1935.

95 Hunter, F. T. Agranulocytosis—Drug or Protein Allergy as a Cause of Agranulocytosis and Certain Types of Purpura, *New England J. Med.* **213** 663, 1935.

96 Schultz, W. Ueber eigenartige Hakerkrankungen, *Deutsche med. Wchnschr.* **48** 1495, 1922.

97 Madison, F. W., and Squier, T. L. Primary Granulocytopenia After Administration of Benzene Chain Derivatives, *J. A. M. A.* **101** 2076 (Dec. 23) 1933.

98 Walter, C. W. Idiosyncrasy to Hexylresorcinol, *J. A. M. A.* **104** 1897 (May 25) 1935.

99 Herz, L. F. The Role of Amidopyrine in the Etiology of Granulocytopenia with Special Reference to Its Chemical Structure, *J. Lab. & Clin. Med.* **20** 33, 1934.

disturbances of the blood Acetanilid, acetphenetidin, salicylic acid and acetylsalicylic acid have somewhat similar chemical structures and may cause violent reactions in sensitive patients Herz' article includes the graphic formulas of many common drugs and is therefore instructive Francis, Ghent and Bullen<sup>100</sup> report the case of a man, aged 27, who died thirty hours after taking 10 grains (0.65 Gm) of acetylsalicylic acid

#### ALLERGIC CUTANEOUS DISEASE

Sulzberger, Wise and Wolff<sup>101</sup> present a tentative classification of allergic dermatoses, the "eczemas," laying stress on atopic dermatitis, with its characteristic distribution and its characteristic reactions comparable to those of hay fever and asthma and often dependent on heredity In cases of atopic dermatitis the exciting cause reaches the skin through the blood stream underneath In contrast to it is contact dermatitis, which is a local sensitiveness of the skin itself, the difficulty being precipitated by direct contact with the offending agent Another type of dermatitis is represented by the reaction to tuberculin and to trichophytin, with its definite clinical picture and with responses which are delayed for twenty-four hours In certain cases the reactions to patch tests, so characteristic of contact dermatitis, have resulted in acneform responses In another paper Sulzberger<sup>102</sup> suggests that acne vulgaris is merely a response to a pilosebaceous irritant which comes from within the body In this way he would explain the eruptions caused by bromide and iodide Tuberculous acne probably belongs in the same category Just how these observations can be correlated with the knowledge that acne is so common at adolescence and therefore is concerned with the gonads is a little difficult Sulzberger suggests, however, that further experiments might demonstrate a hypersensitiveness of the pilosebaceous apparatus to various hormones, and the effect is therefore something more than simple stimulation of the apparatus by these same hormones

Hill<sup>103</sup> gives an excellent review of his study of 900 cases of eczema in infants and young children, most of them in the group of atopic dermatitis If the exciting cause is borne by the blood there is no reason that the conception of it should be limited to foods Dusts which are

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100 Francis, N., Ghent, O. T., and Bullen, S. S. Death from Ten Grains of Aspirin, *J. Allergy* **6** 504, 1935

101 Sulzberger, M. B., Wise, Fred, and Wolf, Jack. Allergic Dermatoses, *J. A. M. A.* **104** 1489 (April 27) 1935

102 Sulzberger, M. B. Acneform Responses to Patch Tests. Follicular and Papulopustular Reactions to Selectively Pilosebaceous Irritants, *Arch. Dermat. & Syph.* **30** 566 (Oct.) 1934

103 Hill, Lewis W. Chronic Atopic Eczema (Neurodermatitis) in Childhood, *J. A. M. A.* **103** 1430 (Nov. 10) 1934

inhaled also reach the blood stream, and in a number of cases it has been possible to show that the outbreak of eczema did bear a direct relation to changes in environment, so pollens, animal danders and the dust of furniture and bedding should always be considered in the etiology of atopic dermatitis. In other cases dusts can cause contact dermatitis. These points are brought out in a second paper by Hill<sup>104</sup> and are illustrated by reports of the cases of the interesting group of patients with contact dermatitis due to pollen.

Brunsting and Anderson<sup>105</sup> report 18 cases of ragweed dermatitis. Their article has excellent pictures. In my experience these patients are easy to cure for because, once the diagnosis is made, treatment with the ether-soluble fraction of the ragweed pollen dissolved in olive oil is so effective that only three or four doses are necessary.

Sensitization of the skin by artificial means has been studied further by Straus,<sup>106</sup> who was able previously to sensitize the skin of new-born infants to poison ivy by direct application of the extract. When drop doses were given by mouth on each of five days symptoms did not result and sensitization by patch test could not be demonstrated later, but when the 10 per cent extract was injected subcutaneously 1 of the 10 infants showed a positive reaction to a patch test. On the whole, however, it can be said that sensitiveness of the skin is produced only by treatment of the skin itself.

The sensitization of guinea-pigs to arsphenamine and other arsenic compounds has given varying results, apparently dependent on whether the experiments were made in Boston, New York or Zurich. The cause of the discrepancy has been unknown and remains so, in spite of the careful controls which Sulzberger and Simon<sup>107</sup> have instituted.

In one experiment Sulzberger and Oser<sup>108</sup> fed their guinea-pigs large amounts of cevitanic acid and noted that the marked increase of vitamin C in the diet did increase the percentage of positive results to some extent.

The grouping of patients with cutaneous disease into one or the other category may be dangerous for the reason that different types

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104 Hill, Lewis W. Sensitivity to Environmental Allergens in Infantile Eczema, *New England J Med* **213** 135, 1935

105 Brunsting, L. A., and Anderson, C. R. Ragweed Dermatitis. A Report Based on Eighteen Cases, *J A M A* **103** 1285 (Oct 27) 1934

106 Straus, H. W. Experimental Study of the Etiology of Dermatitis Venenata, *J Allergy* **5** 568, 1934

107 Sulzberger, M. B., and Simon, F. A. Arsphenamine Hypersensitiveness in Guinea Pigs, *J Allergy* **6** 39, 1934

108 Sulzberger, M. B., and Oser, B. L. Influence of Ascorbic Acid of Diet on Sensitization of Guinea Pigs to Neoarsphenamine, *Proc Soc Exper Biol & Med* **32** 716, 1935

of dermatitis may occur together in the same patient. A patient with an atopic type of sensitiveness may also have a skin which is susceptible to reaction on direct contact, and it is with this idea that the use of patch tests, even in typical allergic dermatitis, has been suggested. On the whole, however, Hill has been unable to confirm the rather enthusiastic reports of Peck and Salomon <sup>109</sup>

Fungous infections of the skin illustrate this point in a different way. Browning <sup>110</sup> expresses the opinion that the symptoms of ringworm are a complication of hypersensitiveness. Many of his patients had other manifestations of allergy besides ringworm, and treatment on the basis of this allergy has brought good results.

Traub and Tolmach <sup>111</sup> treated 135 patients having dermatophytosis with intradermal injections of trichophytin. Apparent cure was obtained in 14 patients, and 58 others showed some improvement, but it is evident that the method leaves much to be desired.

In the meantime, Adamson <sup>112</sup> suggests that psoriasis has a possible allergic background. He collected the scales from psoriatic lesions, washed them with ether and then made various extracts in watery saline solutions. Intradermal tests with these extracts caused a negative reaction in 10 persons with normal skin but caused a positive reaction in each of 6 patients with psoriasis. The apparent sensitiveness could not be transferred to a normal recipient.

#### OTHER MANIFESTATIONS OF ALLERGY

*Migraine*—Vallery-Radot and Hamburger <sup>113</sup> have an excellent article on the probable physiology of migraine. Scotoma, transient palsy and hemianopia suggest a definite lesion in the cortex, perhaps near the optic chiasm. Moreover, the average attack is short, and the lesion must therefore be "reversible" and not a true destruction of the tissue. Other studies concern the direct observation of the cerebral arteries following attempts to produce spasm or dilatation by drugs. In addition, the authors review the literature on the sympathetic system, pointing out that the cerebral circulation as a whole has a regulator mechanism con-

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109 Peck, S. M., and Salomon, G. Eczema of Infancy and Childhood, I. Contacts as Etiologic Agents, with Particular Reference to Feathers, *Am J Dis Child* **46** 1308 (Dec.) 1933.

110 Browning, W. H. Ringworm of Extremities Due to Allergic Unbalance, *New Orleans M. & S. J.* **87** 747, 1935.

111 Traub, E. F., and Tolmach, J. A. Dermatophytosis. Its Treatment with Trichophytin, *Arch. Dermat. & Syph.* **32** 413 (Sept.) 1935.

112 Adamson, W. B. Psoriasis as Possible Allergic Manifestation, *J. Allergy* **6** 294, 1935.

113 Vallery-Radot, P., and Hamburger, J. Pathogénie de la migraine, *Biol. med. Paris* **24** 235, 1934.

trolled chiefly by the cervical portion of the sympathetic system. If the sympathetic trunk is severed on one side the regulator mechanism no longer functions, and under these conditions epinephrine can produce a much greater vasoconstrictor action. Certain drugs, such as ergotamine, which affect the sympathetic nervous system can in this way enhance the action of epinephrine.

These observations find some confirmation in the studies from Forbes' laboratory at Harvard. Here, Finley<sup>114</sup> made trephine holes in the skull of sensitized guinea-pigs and then made direct observations on the changes in caliber of the pial vessels during anaphylactic shock. His observations are contrary to expectation because during shock the pial vessels showed no constriction but definite dilatation and cyanosis, and this effect was specific, because the injection of serum into nonsensitive animals produced no such change. Later however, this dilatation proved to depend not on anaphylaxis but on asphyxia, because in another experiment the clamping of the trachea resulted in a similar change in the pial vessels.

Foster Kennedy<sup>115</sup> has already laid stress on various focal symptoms, not only in migraine but following the use of therapeutic serums. New laboratory studies confirm the conclusions which Kennedy drew from his clinical observations, namely, that edema of the brain is often localized.

Vaughan<sup>116</sup> continued his clinical study of migraine. Fifty-one of his patients were relieved to a considerable extent by the elimination of specific foods and dusts, according to the methods of clinical allergy.

Epilepsy is, in many respects, analogous to migraine, and Forman<sup>117</sup> reports 10 cases in which the attacks of unconsciousness were found to depend on sensitiveness to a specific food.

Urticaria. Fink and Gay<sup>118</sup> report on 170 patients with urticaria whom they have followed for from two to ten years. Urticaria due to cold is an interesting condition, heretofore shrouded in some mystery.

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114 Finley, K. H. Changes in Caliber of Pial Vessels in Guinea Pigs During Anaphylactic Shock, *J Immunol* **27** 169, 1934.

115 Kennedy, Foster. Migraine. A Symptom of Focal Brain Edema, *New York State J Med* **33** 1254 (Nov 1) 1933, *Nervous Complications Following the Use of Therapeutic and Prophylactic Serums*, *Tr Am Neurol A*, 1928, p 410.

116 Vaughan, Warren T. An Analysis of the Allergic Factor in Recurrent Paroxysmal Headaches, *J Allergy* **6** 365, 1935.

117 Forman, J. Atopy as Cause of Epilepsy, *Arch Neurol & Psychiat* **32** 517 (Sept) 1934.

118 Fink, Arthur I., and Gay, Leslie N. A Critical Review of One Hundred and Seventy Cases of Urticaria and Angioneurotic Edema Followed for a Period of from Two to Ten Years, *Bull Johns Hopkins Hosp* **55** 280, 1934.

Levine<sup>119</sup> reviews the literature with considerable care. The cases fall into two groups: in one the sensitiveness is a purely local phenomenon of the skin, and in the other the cutaneous manifestation is simply a part of an underlying systemic disturbance, the lesions representing an aggravation of Lewis' triple response. In spite of his systematic study, however, Levine is bound to confess that he could not apply his knowledge to all the cases at hand and he could not place all of them in one group or the other.

*Other Symptoms*—Other symptoms have been linked with allergy. Ryle<sup>120</sup> describes certain abdominal and circulatory disturbances to which the theories of allergy might have application, especially if certain postulates are fulfilled. These postulates include evidence of allergy in the family background, other allergic manifestation in the patient, such as cutaneous lesions, hay fever or asthma, or perhaps simply that the patient knows of his idiosyncrasy to some food, drug or extraneous substance and, finally, some evidence that the symptoms, however bizarre, do come and go in accordance with changes in environment or diet.

Freedman<sup>121</sup> reports another case of anaphylactic shock. A boy, aged 6 years, with a history of asthma and eczema, was given diphtheria antitoxin. On the sixth day, severe asthma developed, and on the ninth day, urticaria. On the twentieth day, the boy came to the clinic, where his sensitiveness to horse serum was tested by the injection of 0.05 cc intracutaneously. In two minutes he was covered with patches of urticaria, and in eight minutes he was dead.

Deissler and Higgins<sup>122</sup> describe the reactions of the whole filled gallbladders of sensitive guinea-pigs when antigen is injected, saying that the pressure in the gallbladder is raised to three times the normal figure. The contraction of the sphincter is evidently greater than that of the rest of the muscle.

Ocular cataracts in young persons were associated with allergy in 3 cases reported from the Mayo Clinic by Daniel<sup>123</sup>

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119 Levine, H. D. Urticaria Due to Sensitivity to Cold. Survey of the Literature and Report of Case with Experimental Observations, *Arch Int Med* **56** 498 (Sept.) 1935.

120 Ryle, J. A. Observations on Abdominal and Circulatory Phenomena of Allergy, *Lancet* **1** 1257, 1935.

121 Freedman, Harold J. Acute Anaphylactic Shock Following Intracutaneous Test for Sensitivity to Horse Serum, *New England J Med* **212** 10, 1935.

122 Deissler, K., and Higgins, G. M. Effect of Anaphylactic Shock on Biliary System, *Proc Staff Meet, Mayo Clin* **9** 678, 1934.

123 Daniel, Ruby K. Allergy and Cataracts, *J A M A* **105** 481 (Aug 17) 1935.

Cleveland White<sup>124</sup> claims that acneform eruptions of the face may depend on hypersensitiveness to a specific food and describes 32 cases in support of his theory

*Reaction to Tobacco*—This problem has been advanced a little further by Chobot,<sup>125</sup> who has collected all the figures from the previous works of Harkavy and Sulzberger. Between 70 and 80 per cent of patients with thrombo-angitis obliterans are sensitive to tobacco, but the trouble is that the controls are likewise sensitive in many instances. Chobot studied the reactions of allergic children to tobacco and found that only 6 of 63, or 11 per cent, gave a negative reaction. All the others (89 per cent) gave a positive reaction in some degree. Passive transfer was attempted with the blood serum of 4 of these children but never with success. An attempt to sensitize guinea-pigs and test the sensitiveness by the uterine strip reaction was negative.

*New Allergens*—The list increases constantly

Karaya gum, used in hand lotions, in printing and especially in fluid for waving hair, has caused a reaction in 2 interesting cases reported by Bullen<sup>126</sup> and Feinberg,<sup>127</sup> respectively.

Chicle in chewing gum caused symptoms and positive reactions in a patient of Kleinman.<sup>128</sup>

Bennett<sup>129</sup> had a patient of 10 years who had the habit of eating paper. The child lost weight, was in poor general condition and later had asthma. At that time, cutaneous tests made with the paper extract caused a positive reaction.

Lycopodium is used in a new powder for an oily scalp, and in a patient whose case is reported by Lambright and Albaugh,<sup>130</sup> perennial hay fever developed from this powder.

Camomile (*Anthemis cotula*) grows throughout the United States as a weed. Rowe<sup>131</sup> had a patient who had a severe rash on his face

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124 White, Cleveland. Acneform Eruptions of the Face. Etiologic Importance of Specific Foods, *J A M A* **103** 1277 (Oct 27) 1934.

125 Chobot, R. The Significance of Tobacco Reactions in Allergic Children, *J Allergy* **6** 383, 1935.

126 Bullen, S. S. Perennial Hay Fever from Indian Gum (Karaya Gum), *J Allergy* **5** 484, 1934.

127 Feinberg, S. M. Karaya Gum Asthma, *J A M A* **105** 505 (Aug 17) 1935.

128 Kleinman, A. I. Allergy to Chicle. Preliminary Report, *J A M A* **104** 455 (Feb 9) 1935.

129 Bennett, T. Case Report. Bronchial Asthma Due to Paper Sensitivity, *New England J Med* **213** 121, 1935.

130 Lambright, G. L., and Albaugh, R. P. Perennial Hay Fever from Lycopodium, *J Allergy* **5** 590, 1934.

131 Rowe, Albert H. Camomile (*Anthemis 'Cotula*) as a Skin Irritant, *J Allergy* **5** 383, 1934.

due to direct contact with this plant Rowe's article contains several good pictures

Gaillardia caused dermatitis in 3 patients whose cases were reported by Rostenberg and Good <sup>132</sup> All three had handled gaillardia flowers

Emeraude perfume caused dermatitis in a patient whose case was reported by Tobias <sup>133</sup>

Dust of insect origin receives continued attention and no doubt should receive more Randolph <sup>134</sup> and MacDermot <sup>135</sup> have each written on the subject of hay fever and asthma dependent on the emanations from May-flies (*Ephemera*)

Two other reports are of more general interest Held and Goldbloom <sup>136</sup> describe the case of a patient with pernicious anemia in whom generalized itching with wheals and subcutaneous swellings developed after the injection of liver extract Later, however, the woman was able to take cooked liver by mouth, and still later, small but increasing doses of liver extract injected subcutaneously each day resulted in a disappearance of the trouble During this treatment, the eosinophil count dropped from 16 to 2 per cent

Simon <sup>137</sup> describes the cases of several patients hypersensitive to pituitary extract, commenting on the fact that like the reaction to lens protein, that to pituitary substance is another illustration of the fact that sensitiveness can develop to a substance present in the patient's own body, that is to say, of homologous origin

#### SUMMARY

During the year, a good deal has been accomplished In the future chemical studies of those substances which produce allergic symptoms to trace the nature of the skin test-active factors still further and to compare them one with another will be helpful Besides that, however, one must know more about the first development of allergy How is

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132 Rostenberg, Adolph, Jr, and Good, C K Gaillardia Dermatitis, J A M A **104** 1496 (April 27) 1935

133 Tobias, Norman Emeraude Perfume Dermatitis, J A M A **104** 1322 (April 13) 1935

134 Randolph, H Allergic Response to Dust of Insect Origin, J A M A **103** 560 (April 27) 1934

135 MacDermot, H E Case Due to May Flies (*Ephemera*), Canad M A J **31** 408, 1934

136 Held, I W, and Goldbloom, A A Addison-Biermer's Anemia (Pernicious Anemia) Report of Case Showing Allergic-Like Phenomena to Liver Extract, J A M A **96** 1361 (April 25) 1931

137 Simon, Frank A Hypersensitiveness to Pituitary Extract, J A M A **104** 996 (March 23) 1935



the body sensitized? By what chemical combination? How and why does the first reaction to contact take place? Infections of the respiratory tract are concerned with this process—there is reason to think of this—but how are the effects achieved? And then, the same old question—Why is it that of all the many persons exposed to a dust, like ragweed pollen, for example, sensitiveness develops in only a few?

After sensitiveness has developed and symptoms occur, what is the treatment? What is the nature of “desensitization”? How long does it last?

These are some of the problems, and the great difficulty is that whatever may be the findings, the results of experiments on animals do not always apply to man and, further, that regardless of what one does, the nature and the degree of sensitiveness in the particular patient are prone to change spontaneously. The hay fever may be outgrown. Any results obtained in allergy, whether experimental or therapeutic, are always hard to control.

# A CRITICAL REVIEW OF THE LITERATURE ON CHRONIC RHEUMATISM

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As the diseases to be discussed are usually designated by the practitioner as chronic rheumatism, this title is chosen. Under this title are two distinct diseases, each differing from the other in etiology, pathology and clinical signs and symptoms. The only points in common are chronicity and involvement of the joints.

As the mortality from either type is practically nil, there are no statistics in this country to indicate the incidence of the two diseases. In England, with its industrial insurance, statistics are available. Glover<sup>1</sup> reported: "In any 1,000 insured males of all ages there will be found one case of rheumatoid arthritis and three cases of osteoarthritis. In any 1,000 insured females of all ages, we should expect three cases of rheumatoid arthritis and two of osteoarthritis." The figures on osteoarthritis include only the cases of persons who consult the panel doctor on account of discomfort from the disease. Its actual incidence is far above that mentioned, as only a small percentage of persons with osteoarthritis suffer from it.

*Antiquity of Chronic Rheumatism.*—Osteoarthritis is the most ancient disease of which there is a record. Moody<sup>2</sup> has called attention to the great frequency of this type of arthritis in the spines of prehistoric animals. As this is a degenerative rather than an infective type of arthritis and as it arises from wear and tear which represents long continued mild trauma or acute trauma to an articulation, its frequency in the skeletons is readily understood.

Not a single instance of rheumatoid arthritis of the extremities was noted in 35,000 Egyptian mummies carefully examined for evidence of disease. Jones<sup>3</sup> reported that practically every adult skeleton showed osteoarthritis of the spine. This can probably be accounted for, at least in part, by the custom of carrying heavy loads on the head. Hrdlička<sup>4</sup> reported the not infrequent presence of osteoarthritis of the spine in ancient Indian remains.

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1 Glover, J. A. A Report on Chronic Arthritis, Reports on Public Health and Medical Subjects, Ministry of Health, no. 52, London, His Majesty's Stationery Office, 1928.

2 Moody, R. L. Paleopathology, Urbana, Ill., University of Illinois Press, 1923.

3 Jones, F. W. J. Archeological Survey of Nubia 2: 26, 1907-1908.

4 Hrdlička, A. J. J. Acad. Nat. Sc. Philadelphia 14: 178, 1909.

## CLASSIFICATION

Confusion in classification has played an important part in retarding the knowledge of this group of diseases. The medical profession has been tardy in recognizing or at least in applying the splendid studies of Nichols and Richardson,<sup>5</sup> who from their exhaustive pathologic studies demonstrated that chronic rheumatism could be divided into two types. They stated: "Our own studies have convinced us that these joint lesions can be divided with great definiteness into two pathological groups: 1, Those which arise from primary proliferative changes in the joints, chiefly in the synovial membrane and in the perichondrium; 2, Those which arise primarily as a degeneration of the joint cartilage." One has the appearance of a chronic infective disease, the other, that of a degenerative disease.

Only in the last decade has a united effort been made in this country to obtain a classification based on pathologic changes and clinical manifestation. The American Committee on Chronic Rheumatism, fathered by Dr. Ralph Pemberton and Dr. Robert Osgood, deserves a great deal of credit for creating an increased interest in this group of diseases.

At the International Congress on Chronic Rheumatic Diseases held at Liège a few years ago, a classification in French, German and English was adopted. The following is the English terminology: (1) rheumatoid arthritis and (2) osteo-arthritis. These terms for the two types have been in common use in England for many years. Synonymous terms for rheumatoid arthritis are infective peri-arthritis, atrophic arthritis and arthritis deformans. Unfortunately, the term arthritis deformans is used in Germany for osteo-arthritis. The term coined by Nichols and Richardson was proliferative arthritis. Hypertrophic arthritis is synonymous with osteo-arthritis. The name given to this type by Nichols and Richardson was degenerative arthritis.

In the present review the terms used for the two diseases are rheumatoid arthritis and osteo-arthritis. Arthrosis is a more accurate descriptive term for this type than arthritis, it was introduced in 1913 by Frederick Muller of Munich and is widely used in Germany. For that reason I have adopted it rather than the term degenerative arthrosis. The simpler the classification, the more readily it will be understood and adopted by the medical profession.

Some German writers subdivide rheumatoid arthritis into a primary and a secondary type. By secondary rheumatoid arthritis they mean the condition that begins as acute rheumatic fever and gradually develops into a chronic type. This form appears to be common in Germany but is rare in this country. As far as I can recall, I have seen only 1 case.

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5 Nichols, E. H., and Richardson, F. S. J. M. Research **21** 144, 1909

## PATHOLOGY

*Rheumatoid Arthritis of the Extremities*—From the standpoint of etiology, emphasis should be placed on the early changes. The later changes may be due to trauma, unequal pressure on the cartilage of the joint or ligamentous traction due to the deformity. This phase of the subject will be discussed later with mixed forms of arthritis.

In the early stage of rheumatoid arthritis there is a round cell infiltration beginning at the junction of the synovial fringe with the articular cartilage. The cellular infiltration gradually extends over the surface of the joint until the whole or only the peripheral portion of the cartilage is covered by a highly vascular membrane resembling granulation tissue. This pannus invades and destroys the underlying cartilage, which is replaced by connective tissue and later by fibrous tissue. Nichols and Richardson stated that not all the cartilage under the pannus is destroyed, circumscribed areas may remain intact.

The round cell infiltration is not confined to the articular surfaces but extends into the periaricular structures and accounts, at least in part, for the characteristic spindle-shaped deformity, best observed in the fingers. In the periaricular structures fibrous changes develop and may be a contributory factor in producing ankylosis.

Simultaneously with the synovial changes, there is marked proliferation due to round cell infiltration of the villi. The slender villous outgrowths later undergo endarteritis obliterans which results in necrosis. In later stages of the disease, polypoid growths (some sessile, others pedunculated) resembling those observed in osteo-arthritis, but rarely so extensive, may develop. Nichols and Richardson stated that such growths may arise from the pannus or from the synovium.

Simultaneously with the round cell infiltration of the synovium, and sometimes subsequent to it, similar round cell infiltration with later formation of connective and fibrous tissue may be observed in the adjacent subcancellous tissue of the epiphysis, and this extends and destroys the adjacent cartilage.

The end-result of the changes in the joint may be fibrous ankylosis or, in case the cartilage is completely destroyed in any area so that the exposed bones come in contact, bony ankylosis. Nichols and Richardson did not study rheumatoid arthritis of the spine.

*Rheumatoid Arthritis of the Spine (Spondylitis Ankylopoietica)*—When rheumatoid arthritis involves the spine, there may develop unusual pathologic changes, largely in the nature of sequelae. As rheumatoid arthritis first involves the synovium and as the intervertebral disk does not have a synovium, the disease attacks the articulation of the transverse processes and the ribs. The pathologic changes are probably the same as those in the extremities. The articulations probably rather early

become ankylosed. As in the extremities, there are early atrophic changes in the involved vertebrae. Later there may be a series of pathologic changes directed toward firm ankylosis of the involved portion of the spine. The sequelae, when they develop, do not appear until considerable time has elapsed. The exact order or sequence of the changes is not definitely known, but they probably appear in the following order: (1) ossification of the intervertebral ligament, especially the anterior longitudinal ligament, (2) invasion by the spongiosa of a vertebra of the adjacent central portion of the disk and penetration through it to the spongiosa in the neighboring vertebra, and (3) possible ossification of the periphery of the disk. The complete structural change creates in the involved portion of the spine an anatomic structure resembling a long bone. The anatomic changes produce a poker spine. The changes are not confined to patients with rheumatoid arthritis. They may arise from other infections. The subject will be discussed under etiology.

*Osteo-Arthritis of the Extremities*—In their investigations of this disease Nichols and Richardson apparently studied only the senescent type, in which changes are due to long continued mild trauma. They did not discuss cases in which the disease arises from acute injury, as for instance the baseball finger. In such cases the damage to the cartilage is followed by a sequence of changes similar to that of the senescent form. Nichols and Richardson did not study osteo-arthritis of the spine, in which another factor is at least largely responsible for the formation of osteophytes. Fisher<sup>6</sup> defined osteo-arthritis as follows: "Osteoarthritis does not constitute a disease sui generis, but is rather the series of physiological or pathological changes that occur in a joint when it is subjected to prolonged or oft-repeated injury, either mechanical or toxic, but of a moderate degree of intensity." He failed to mention that acute severe injury may give rise to similar changes.

Normal cartilage on bending shows striae. Nichols and Richardson reported that the earliest lesion was fibrillation of the cartilage. Fibrous tissue forms in the striae, and this results in a ridging of the cartilage, followed in turn by vertical cracking. The changes are most marked in the central cartilage of the surface of the joint, due probably to poor nutrition, as the cartilage does not contain blood vessels and is nourished by diffusion. Following the fibrous changes there is irregular degeneration of the cartilage, which gives a pitted appearance to the surface. The bottom of the pit may show exposed bone. The intervening area of intact cartilage may proliferate and later show ossification. The peripheral cartilage may remain normal for years after the central degeneration. Sooner or later, however, there is cartilaginous hyperplasia,

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<sup>6</sup> Fisher, A. G. B. *Chronic (Non-Tuberculous) Arthritis*. New York, The Macmillan Company, 1929, p. 192.

which results in lipping, and later ossification develops which gives rise to osteophytes, which characterize this type of arthritis. Fisher expressed the opinion that the proliferation of the peripheral cartilage is a physiologic response to increase the surface of the joint.

In contradistinction to rheumatoid arthritis, changes in the synovium appear late and take the form of villous proliferation. Existing villi become hypertrophied, and many new villi arise from the synovium. Chondromas may develop in the villi. These may later become detached and give rise to loose bodies. Their presence may account for the recurrent synovitis seen in patients with this condition. The crunching sounds heard in cases of osteo-arthritis of the knee are due largely to rubbing together of the villi.

Bony or fibrous ankylosis is practically unknown. Atrophy of muscle and skin is not present, nor is there ischemia of the skin.

When the central cartilage is acutely injured it undergoes necrosis. Fisher shaved a very thin layer of central cartilage from a rabbit's knee and several weeks later killed the animal. He observed that the periphery of the articulation showed cartilaginous lipping and that the central cartilage was necrotic. Injury of the cartilage by other means, as by the injection of acid, will produce similar changes. Osteo-arthritis can be produced readily experimentally, but no one has been able to produce experimental rheumatoid arthritis.

*Osteo-Arthritis of the Spine*—Osteo-arthritis of the extremities has its origin in the articular cartilage. The intervertebral disk has only a thin fibrocartilaginous plate between it and the vertebra. The pathology of this type of arthritis when it involves the spine requires separate attention.

The most important pathologic studies of the disease have been made in Germany. Schmorl and Junghans,<sup>7</sup> with their careful study of 10,000 spines removed at autopsy, have supplied a valuable fund of information. The monograph of Anton Fischer has summed up, and added to, the knowledge of the condition. I<sup>8</sup> recently discussed the present knowledge of the subject.

Jones<sup>9</sup> made a careful study of the spines of a large number of natural mummified Nubian remains. His observations have since been confirmed by Schmorl. He took the position that the osteophytes develop not on the rim of the vertebra but slightly above and corresponding to points of attachment of the fibers of the anterior longitudinal ligament.

7 Schmorl, G., and Junghans, H. Die gesunde und kranke Wirbelsäule im Roentgenbild, Leipzig, Georg Thieme, 1932.

8 Miller, Joseph L. Chronic Rheumatic Diseases of the Spine, Arch Int Med **54** 161 (Aug.) 1934.

9 Jones,<sup>3</sup> p. 271.

The spine of man has not adjusted itself to the upright posture, as is shown by the pathologic changes which develop with increasing years.

The intervertebral disk is made up of two closely related but somewhat different structures, the annulus fibrosus and the nucleus pulposus. They function as shock-absorbers and also assist in the rotation of the spine. Both of the structures are formed by interlacing fibrous tissue, with a mucoid fluid in the interspaces. Both begin to show degenerative changes as early as the third decade of life. Schmorl noted that 10.7 per cent of the spines removed from bodies of persons between 20 and 30 years of age showed evidence of pathologic changes.

The earliest degenerative changes in the disk are noted in the nucleus pulposus. It loses its fluidity, and the fibers become desiccated and finally disintegrate. The elastic ball is replaced by a solid mass, which may later become calcified.

Somewhat later the annulus undergoes similar degenerative changes. As a consequence of these changes the disk becomes thinned and loses its resiliency. Under normal conditions the fibers of the annulus play an important rôle in the fixation of the vertebra. There is increased mobility of the vertebra, with the destruction of the annulus. Schmorl stated that he has never seen osteophytes adjacent to a normal disk. The increased mobility of the vertebra is the most important etiologic factor in the formation of osteophytes. Rarely does mere impingement of the vertebra account for the formation of spurs. The increased mobility causes increased traction on the intervertebral ligaments, especially the anterior longitudinal ligament. As a result of the strain, periosteal trauma occurs at the points where the fibers are attached to the bone. It is in this region that osteophytes develop. Not infrequently one finds bony spurs along the entire course of the insertions of a ligament, evidence that traction as well as pressure may be responsible for osteoarthrosis. Acute trauma to a vertebra or sudden severe damage to a disk may be responsible for the formation of osteophytes.

Anton Fischer has expressed the opinion that the formation of osteophytes on a vertebra is a physiologic response directed toward reconstruction of a spine which has become functionally inefficient. The primary objective is to effect a bridging of the interspace between the vertebrae and render the spine rigid.

Osteomyelitis of a vertebra following typhoid may be followed later by a growth of osteophytes from the damaged and adjacent vertebrae, which results in complete bridging. Dr. Hollis E. Potter showed me a roentgenogram in a case in which the development of such changes had been followed by repeated roentgen observations of the spine.

From these findings one may conclude that a poker spine following typhoid may be due to spondylitis ankylopoietica or to localized bridging by osteophytes, which arise as a result of osteomyelitis of a vertebra.

*Calcium Metabolism*—Hastings and Greene<sup>10</sup> made determinations of the calcium content of the blood in 50 cases of rheumatoid arthritis and 50 cases of osteo-arthritis. In the cases of rheumatoid arthritis the calcium content was normal, in the cases of osteo-arthritis there was a slight reduction, which the authors thought might be due to the greater average age of the patients.

*Cholesterol*—Hastings and Bruger<sup>11</sup> observed that the total cholesterol content of the blood tends to be slightly reduced in rheumatoid arthritis and increased in osteo-arthritis. The authors venture the opinion that this is evidence that rheumatoid arthritis is of infective origin and osteo-arthritis of degenerative origin.

#### ETIOLOGY

*Rheumatoid Arthritis*—The presence of round cell infiltration in the synovium in the early stages of the disease is evidence that rheumatoid arthritis is an inflammatory disease of probable bacterial origin.

A number of observers have made sedimentation tests on the blood and have noted a positive reaction in a high percentage of cases. The same group noted a negative reaction in cases of osteo-arthritis. Dawson and Boots<sup>12</sup> reported that the sedimentation rate parallels to a high degree the severity and extent of the arthritic process.

Dawson and Olmsted<sup>13</sup> have made careful studies of the agglutination reaction in 66 cases of rheumatoid arthritis and have also carried out tests in a series of controls. In cases of active rheumatoid arthritis the serum agglutinated in a high titer all strains of hemolytic streptococci. The authors observed that the special hemolytic streptococcus isolated by Cecil from the blood stream was not agglutinated in a higher titer than other strains. In 50 controls (18 cases of osteo-arthritis) agglutination occurred in 2 and only in a low titer. Thirty-one strains of other organisms failed to be agglutinated.

Dawson, Olmsted and Jost<sup>14</sup> made a comparative test of agglutinins and precipitins against hemolytic streptococci in 71 cases of rheumatoid arthritis. They noted a close but not absolute agreement in the capacity of serum from patients with rheumatoid arthritis to agglutinate and precipitate various strains of hemolytic streptococci. Of the controls agglutination occurred in only 5 per cent in a titer of 1:160.

There is abundant clinical evidence that the disease is infective. Still's disease (which is rheumatoid arthritis of childhood) causes not

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10 Hastings, E. F., and Greene, C. H. *J. Lab. & Clin. Med.* **20** 929, 1935.

11 Hastings, E. F., and Bruger, M. *J. Lab. & Clin. Med.* **20** 675, 1935.

12 Dawson, M. H., and Boots, R. H. *New England J. Med.* **208** 1030, 1933.

13 Dawson, M. H., and Olmsted, W. *J. Immunol.* **29** 189, 1932.

14 Dawson, M. H., Olmsted, W., and Jost, E. L. *J. Immunol.* **27** 385, 1934.



only marked inflammation of the joints but also fever, leukocytosis, lymphadenitis and frequently enlargement of the spleen. The disease in adults is more insidious in onset but nevertheless presents evidence of an inflammatory reaction. The course of the disease, with remissions and later recurrences, speaks for its infective origin.

The problem of positive results of blood cultures is a moot question. Some competent bacteriologists have obtained positive results of cultures in 60 per cent of cases.<sup>15</sup> There are many other reports of positive results in a high percentage of cases. On the other hand, an equally qualified group has been unable to obtain any or at most a negligible number of positive results.

It is significant that with, I believe, only one exception the micro-organism obtained was *Streptococcus viridans*. There is considerable evidence, which will be considered later, that the disease may be due to infection with *Streptococcus haemolyticus*. It is somewhat significant that in the past two years there is a dearth of reports of positive results of cultures. While it cannot be decided positively at this time, there is accumulating evidence that positive results were probably due to wrong interpretations or errors in technic.

The primary source of infection in rheumatoid arthritis is still a moot question and will be discussed under treatment.

It has been suggested that the disease might be allergic. It is impossible, I believe, to explain the pathologic process on an allergic basis.

There is some evidence that a previous attack of acute rheumatic fever is a predisposing factor. There is considerable evidence that there is some relationship between the diseases. In 25 per cent of patients with rheumatoid rheumatic arthritis Dawson<sup>16</sup> noted subcutaneous nodules identical histologically with those observed in cases of acute rheumatic fever. This is approximately their incidence in cases of acute rheumatic fever. Glover in his report stated that 18 per cent of patients with rheumatoid arthritis give a previous history of acute rheumatic fever, but 14 per cent of patients with osteo-arthritis also give a history of acute rheumatic fever.

It is generally reported that the disease is much more frequent in females. Anton Fischer, in his large clinic at Aachen, noted that the two sexes were equally affected.

In the Glover report it was stated that the investigators were unable to find that occupation played a rôle in the incidence of the disease. There is some difference of opinion as to whether or not heredity plays a rôle.

Climate plays an important rôle in the incidence of both acute rheumatic fever and rheumatoid arthritis. They are both diseases of north

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15 Cecil, R. L., Nichols, E. E., and Stainsby, W. J. *Am J M Sc* **181** 12, 1931.

16 Dawson, M. J. *J Exper Med* **57** 845, 1933.

temperate zones In the southern states both of the diseases are of infrequent occurrence Coburn and Paul<sup>17</sup> reported that children in New York who were subject to annual attacks of acute rheumatic fever were free from recurrence when living in Puerto Rico In New York, while the nasopharynx was free from hemolytic streptococci in summer, the organisms appeared in late autumn and winter In the tropics at sea-level there is a very low incidence of scarlet fever This is the case, for example, at Rio de Janeiro In the same latitude at an elevation of 3,000 feet its incidence is considerably greater Nichol<sup>18</sup> stated that during a period of five years only 4 cases of acute rheumatic fever were observed at the Miami General Hospital, although 31,158 patients were admitted during this period

Clarke<sup>19</sup> has made a complete review of the incidence of acute rheumatic fever in the tropics He practiced for thirty-three years in India and during this period examined 150,000 patients, but he never saw a patient with mitral stenosis, acute rheumatic fever or chorea He also registered the births and deaths for a period of years In 97,000 death certificates, acute rheumatic fever was never recorded Clarke has carried on correspondence with pathologists in the tropics, one of whom had performed 600 autopsies and had never noted mitral stenosis

Freund<sup>20</sup> reported that in 42 per cent of 110 cases of rheumatoid arthritis the condition directly followed acute rheumatic fever or the patient gave a history of having had that disease

Anton Fischer observed 201 cases of secondary rheumatoid arthritis In 65 per cent the disease was directly engrafted on acute rheumatic fever The acute inflammation never completely cleared up, and gradually there developed the signs and symptoms of rheumatoid arthritis In the remaining 35 per cent the acute disease subsided and was followed after a brief interval by rheumatoid arthritis Valvular heart lesions developed in 60 per cent of this group It is Fischer's opinion that the presence of valvular lesions in persons with rheumatoid arthritis is usually due to an antecedent attack of acute rheumatic fever

*Osteo-Arthrosis*—This is a degenerative disease due to long continued mild trauma, to acute trauma or to ligamentous traction In the spine the acute trauma may be osteomyelitis of a vertebra Here, gradual impairment of the disk leads to greater mobility of the vertebra, and this results in increased traction on the intervertebral ligament Traction is the chief factor responsible for osteo-arthritis of the spine Acute damage to the disk or vertebra (whether this is due to external injury or to infection) is responsible for localized osteo-arthritis of the spine

17 Coburn, A. F., and Paul, R. H. *J. Exper. Med.* **56** 609, 1932

18 Nichol, E. S. *Am. Heart J.* **9** 63, 1933

19 Clarke, J. T. *J. Trop. Med.* **33** 249, 1930

20 Freund, Ernest. *Gelenkerkrankungen*, Berlin, Julius Springer, 1929, p. 75

In the extremities all three of the factors, either singly or combined, may be responsible for the changes in the joint. Acute damage to an articulation at any age may be followed by osteo-arthritis. I recently examined a young woman who at the age of 17 years had frozen the index and middle fingers on the right hand. They were so badly damaged that amputation was considered. However, the circulation returned, and the fingers were saved. The two fingers never grew in length, apparently owing to severe damage to the growth center in the epiphysis. Furthermore, osteo-arthritis developed in the middle and terminal articulations of these fingers, probably owing to damage by freezing of the articular cartilage.

Overweight is the most frequent cause of osteo-arthritis of the knee. This is met with especially in women at the menopause who have gained weight rapidly. It is frequently mentioned that this suggests an endocrine etiology of the disease. An endocrine disturbance probably accounts for the gain in weight but not directly for the osteo-arthritis. I have examined two young, slender women with osteo-arthritis of the knees. In both instances there had been severe injury of the knee, which was followed by synovitis. Osteo-arthritis was caused later, I believe, by acute injury and resulting damage to the cartilage.

The so-called gonorrheal spur on the os calcis is sometimes referred to as evidence that osteophytes may be due directly to an infection. The term gonorrheal spur is a misnomer. Gonorrhea is a widespread disease. When a person who contracted gonorrhea in his youth later shows a spur on the os calcis, it would be an error to conclude that it was of gonorrheal origin. Spurs develop on the os calcis at the point of attachment of the plantar fascia. There are then two factors, pressure and traction, both recognized as etiologic factors in the formation of osteophytes. It has been demonstrated that men who stand a great deal, such as motormen, conductors, dentists and barbers are especially prone to the development of osteophytes on the os calcis.

#### SIGNS AND SYMPTOMS

*Rheumatoid Arthritis*—In adults the disease rarely is marked by an acute onset. In children the onset is usually acute and at times is not readily differentiated from acute rheumatic fever. In adults the onset is usually insidious, with migratory pains in the joints or slight stiffness of the fingers preceding definite inflammation in the articulation. There is a tendency to symmetrical involvement. Most frequently the fingers and wrists are first involved, next in frequency is the knee, eventually all articulations in the extremities may be affected and, in addition, the articulations of the jaw. The joints become tender, slightly swollen and painful on motion. A characteristic spindling of the midarticulation

of the fingers marks the disease. The hands become cold and clammy. The skin, because of atrophy, becomes smooth and shiny as the disease advances.

There is selective muscle atrophy, which is an important factor in the marked deformities observed in the advanced stages. The cause of this particular group of changes—coldness of the extremities, atrophy of the skin and selective muscle atrophy—is, I believe, unexplained. The coldness of the extremities and atrophy of the skin are probably due to ischemia, but no satisfactory explanation has been found for the ischemia. The selective muscle atrophy has not been satisfactorily explained. It may continue to progress after all evidence of inflammation in the articulations has subsided. Eight years ago I observed a patient with rheumatoid arthritis confined to the hands which had been present for one year. Aside from the swellings of the joints, there was no deformity. The patient was given five intravenous injections of typhoid vaccine, and the inflammatory symptoms, including pain, promptly subsided. He has not had a recurrence. He plays golf and goes duck shooting each autumn. During this period there has gradually developed marked ulnar deviation of the hand, a common type of deformity in this disease. If the disease progresses, fibrous or bony ankylosis and muscular contractions develop, which cause a marked deformity. Subcutaneous rheumatic nodules, especially in the region of the elbow, may appear. The course of the disease is extremely variable, and for this reason the results of treatment are of little value unless an untreated control series is observed. In the mild cases, even after years, the disease may not progress. Furthermore, the disease is characterized by remissions, when the improvement is marked or when the symptoms of activity may disappear entirely. Apparently the infection has been spontaneously controlled or obliterated. The question can be raised as to whether or not the recurrences might be due to activation of a chronic latent infection. In a recurrence the symptoms may develop rapidly, and within a few days the involved joints may become painful and tender. This sudden development of acute symptoms would not fit in well with the activation of a latent infection. Furthermore, such a recurrence frequently follows an acute infection of the upper respiratory tract. Later the symptoms may (and usually do) recur, because of reinfection, I believe. The infection dies out in a joint which has become ankylosed because of the complete obliteration of the synovium, the soil on which the micro-organism thrives.

Roentgenograms made during the early stages show only increased porosity of the end of the long bone adjacent to the involved joint. The cause of the early atrophy of the bone, which is akin to atrophy of the skin and muscles, has not been explained satisfactorily. Later, roentgenograms show a narrowing or obliteration of the interarticular space,

which is caused by destructive changes. Swelling of the regional lymph glands is often present. Only in the acute cases is the spleen palpably enlarged. There is usually a moderate degree of secondary anemia.

Is rheumatoid arthritis ever responsible for valvular cardiac involvement? It is reported that from 5 to 10 per cent of patients with the disease have a cardiac murmur. I cannot recall a single instance in the literature in which it was definitely determined that mitral stenosis actually appeared during the course of the disease. If a mitral regurgitant murmur develops, the question should still arise as to whether the murmur is due to involvement of the leaflets or to impairment of the heart muscle. The development of mitral stenosis during the course of the disease would be acceptable evidence that rheumatoid arthritis can be responsible for a valvular lesion. A considerable number of the patients have previously had acute rheumatic fever, chorea or scarlet fever, which might have been responsible for the stenosis.

Anton Fischer stated that in cases of secondary rheumatoid arthritis 65 per cent of the patients had valvular lesions. He had never noted a valvular lesion in a case of primary rheumatoid arthritis.

Rarely is there great difficulty in making a diagnosis except in those cases in which indefinite neuralgic pains and perhaps slight stiffness of the joints alone are present.

*Rheumatoid Arthritis of the Spine*—One must bear in mind that in only a small percentage of cases is spondylitis ankylopoietica due to the infection responsible for rheumatoid arthritis. The gonococcus is responsible in a large percentage of cases. While the hip joint is rather infrequently involved in rheumatoid arthritis, it is frequently involved when the disease attacks the spine. The hip joint was involved in 19 per cent of Anton Fischer's cases. The sacro-iliac articulation is also frequently involved. In a case of rheumatoid arthritis, with its insidious progress, the patient may complain very little of his spine. His only complaint may be of slight but gradually increasing rigidity with some pain in the nerve roots. Pressure along the spine may be painful. As the articulations of the ribs become ankylosed, the respiratory expansion of the chest is reduced. Roentgenograms of the spine may show obliteration of the interarticular spaces at the articulations of the transverse processes. When the pathologic changes progress to make a complete picture, there is characteristic "bamboo-stick" spine.

When the onset is acute, as is usually the case when the infection is due to the gonococcus, the pain along the spine and the nerve roots posteriorly may be intense. The pain in the nerves is thought to be due to direct involvement of the root as it comes into close proximity with the lateral articulations of the spine.

*Osteo-Arthrosis of the Extremities*—The Heberden node is as a rule slightly tender to pressure and bending. If the node develops

rapidly, it may be quite tender. This is probably due to displacement of the soft tissues. The articulation which is most troublesome is the knee. Pathologic changes in this joint are noted most frequently in women who are overweight and especially in those in whom the obesity has developed rapidly, as, for example, after the menopause. The first symptom is usually stiffness, with perhaps slight pain on rising from a sitting posture. Later, the knees are very painful when the patient goes up or down stairs. This is due to the increased weight borne by the articulation. Standing, unless prolonged, is rarely painful. Walking on the level may not be painful.

All are so familiar with the appearance of a Heberden node that a description is unnecessary. Examination of the knee frequently shows some puffiness due to traumatic synovitis. Tenderness is not marked. By holding one hand on the knee cap and having the patient swing the leg, a crunching sensation can usually be elicited. A roentgenogram of the knee may not show a formation of spurs, as they are often very slow in forming.

In this discussion only the knee and fingers have been mentioned. In the elbow and shoulder the chief symptom is pain on making certain movements. The diagnosis of osteo-arthritis in the shoulder can best be made by a roentgenogram, as a subacromial bursitis may cause similar symptoms. Osteo-arthritis does not cause ankylosis, although some restriction in movement may be present.

*Osteo-Arthritis of the Spine*—Osteo-arthritis of the sacro-iliac articulation may develop as a result chiefly of traction caused by sacro-iliac slipping. Osteo-arthritis of the spine is more troublesome and may produce a greater degree of disability than osteo-arthritis of the extremities. The chief symptoms are due to pains in the nerve roots—in the sacral, lumbar, dorsal, occipital and cervical portions. The etiology of these pains is not clear. Anton Fischer stated positively that the pains in the roots are not directly or indirectly due to the osteophytes. He attempted to explain the discomfort as being due to other factors, but his arguments are not very convincing.

Osteo-arthritis of the spine is almost universal in persons past 60 years of age. Schmorl has removed 10,000 spines at autopsy and has carefully examined 4,253 spines (practically equally divided between the sexes) for osteophytes. He reported that osteo-arthritis was not noted in the spines of subjects under 20 years of age. Between the ages of 20 and 29 it was present in 36.3 per cent, between the ages of 40 and 49, in 77.8 per cent, between the ages of 60 and 69, in 95 per cent, and between the ages of 70 and 79, in 97 per cent. There was only a slight difference at the various age periods in the two sexes.

With this high incidence, it is apparent that osteo-arthritis of the spine only occasionally causes discomfort. Rarely does it cause a high

degree of permanent disability and then only for persons in special occupations. It is responsible, however, for many aches and pains and for considerable worry on the part of the patient, who fears that he has a disease which may cripple him.

#### MIXED FORMS

The presence of rheumatoid arthritis and osteo-arthritis in the same patient has been a stumbling block in the classification of chronic rheumatism. This has even led some physicians to express the opinion that the two types of chronic rheumatism are closely related. One is able to explain most, if not all, the mixed forms if one admits that acute trauma, long continued mild trauma and ligamentous traction are etiologic factors in osteo-arthritis. The presence of osteo-arthritis in conjunction with rheumatoid arthritis does not mean that the osteophytes are a direct result of rheumatoid arthritis or are indirectly due to infection.

As a result of acute trauma or long continued mild trauma the patient may have had osteo-arthritis preceding the onset of the rheumatoid arthritis. More frequently, however, the deformity produced by the rheumatoid arthritis causes unequal pressure on the articular surface and increased ligamentous tension. Ulnar deviation of the hand, a frequent deformity in rheumatoid arthritis of the wrist and hand, is frequently associated with the presence of osteophytes on the involved joints. Unequal pressure can cause osteophytes to appear on the concave side of the deformity, and ligamentous traction can explain their presence on the convex surface.

I have seen marked osteo-arthritis of the spine of a child of 12 years who was so crippled by rheumatoid arthritis that she walked in a crouching posture. The deformity arising from rheumatoid arthritis of the ankle or foot can be responsible for osteo-arthritis of the corresponding knee. While one may not be able in all cases to explain osteo-arthritis associated with rheumatoid arthritis, this is not an argument that rheumatoid arthritis can be directly responsible for the formation of osteophytes. Another questionable etiologic factor in the mixed type of arthritis is the impairment of circulation noticed especially in the skin—a possible factor in degeneration of the cartilage.

#### PROGNOSIS

*Rheumatoid Arthritis*—Rheumatoid arthritis is inconspicuous as a cause of death, but it may be very expensive to the community when impoverished patients require hospital care. It is responsible for great physical discomfort and mental anguish. A specific form of treatment that will promptly terminate the disease in a high percentage of cases has not been developed. Even if such a type of treatment were found

it would not prevent recurrences of the infection. This is a problem almost, if not quite, as great as that of destroying an active infection in this disease. The course of the disease is so extremely variable and a remission is so uncertain that while it may be used by the physician to encourage the patient, he is never able to predict when such a remission may occur.

*Osteo-Arthrosis*—The physician can assure the patient that the probability of more than a moderate degree of disability is slight. It is true that it may disable a laborer for his particular vocation. In persons whose work requires heavy lifting, osteo-arthritis of the lumbar portion of the spine may disqualify them for their particular jobs. With few exceptions, however, it may be considered as a painful but not a disabling disease.

#### TREATMENT OF RHEUMATOID ARTHRITIS

Sir William Osler said: "In treatment the placid faith of the believer, not the fighting faith of the aggressive doubter, is our besetting sin." This statement, I believe, may well be applied to the therapy of rheumatoid arthritis in the past.

It is the aggressive doubter who insists that the control method be used. Rheumatoid arthritis is a disease the onset and course of which are extremely variable. Spontaneous remissions are not uncommon, and such remissions may reach the point where all evidence of infection has subsided. In deciding whether or not improvement has followed a certain course of treatment, such improvement to be convincing should occur shortly after the treatment is instituted. Emphasis must be placed on the objective observations. A patient with an enthusiastic physician standing at his side after an operative procedure (whether it is the extraction of a tooth or the use of vaccines) is not in a state of mind to give reliable information as to the way he feels.

The first essential in successful treatment of the disease is early diagnosis, before contractures or ankylosis has developed. When these complications have appeared, while the deformity in many cases can be corrected to a certain degree, the patient rarely can expect more than a considerable degree of improvement in his condition.

The aim of treatment is (1) to destroy the infection in the diseased joints, (2) to prevent contractures and ankylosis, and (3) to prevent reinfection.

Unless improvement is prompt after any method of treatment, the question may be raised as to whether the condition became better as a result of treatment or whether the improvement was due to a spontaneous remission. Any special treatment extending over months increases the chances of a spontaneous remission. The improvement in the patient's condition must be objective. Before the treatment is started



a careful report should be made of the joints involved and the degree and character of the pathologic changes

The patient with a painful crippling chronic disease has faith in a magic wand that will restore his health. The patient has temporary faith in each new method of treatment and will declare he is benefited, even though examination of the joints fails to confirm the statement. An enthusiastic physician may acquire at least a temporary reputation for great skill. The psychic effect of treatment must always be borne in mind before drawing conclusions. The head of the department of medicine in a state university, wishing to make cultures from lymph glands adjacent to involved joints, sent patients to the hospital for removal of a gland. He told me that on the day following some of the patients told him how much they had been benefited by the minor surgical operation and demonstrated by movements that the treatment had been a great success. Many instances of the psychic effect of simple procedures have come to my attention. A woman with brachial neuralgia recently consulted me. One month previously she had consulted a physician, who told her the pain was due to arthritis. A roentgenogram was made, an abscessed tooth was found, and the patient was told that this was the cause of the trouble. The tooth was extracted, and by the time the patient reached home the pain had subsided. Three days previous to the time she consulted me she read of the death of a man of arthritis, her pain immediately returned.

There is, I believe, only one method of procedure which is at all dependable, namely, the use of controls. The controls must have the benefit of psychic influence, for instance, the use of measures which cannot possibly modify the disease but which add to the patient's hope. No doubt the thousands of persons who claim to have been benefited by Locke's manipulative treatment owe their improvement to faith.

Of the means employed to fight the infection, two will be discussed: vaccines and fever therapy.

Since the introduction of vaccine therapy, it has been used extensively in the treatment of rheumatoid arthritis. As the specific micro-organism of rheumatoid arthritis is undetermined, the vaccine used may be considered nonspecific. Most of the vaccines used have contained streptococci. Many of the reports on the use of vaccines in the treatment of this disease are of no value because no attempt has been made to separate the two types of rheumatism. Often when the physician has recognized two types of rheumatism and has treated the infective type, no attempt has been made to use controls. Dawson and Boots<sup>12</sup> administered treatment with various vaccines in 2,000 cases of rheumatoid arthritis. The controls were given subcutaneous injections of isotonic solution of sodium citrate, a wise procedure, as each group received subcutaneous injections. The investigators concluded that the value

of vaccine therapy in the treatment of this disease has not been proved. Remissions occurred with equal frequency in those receiving vaccines and in the controls. The workers were not able to modify the sedimentation rate with vaccine therapy.

Fever therapy, produced by the intravenous injections of the organisms of typhoid, has been in use in the treatment of this disease for more than twenty years. More recently, various other methods of raising the body temperature have been introduced. The results of this method of treatment indicate that it has some value. As the results are immediate, spontaneous remissions can be excluded. Recently, Short and Bauer<sup>21</sup> raised the body temperature by means of diathermy to 104 F and maintained the temperature at this point for four hours. Eighty per cent of the patients had temporary relief, but in only 20 per cent was the relief maintained during the period of follow-up (from one month to one year). The results of these investigators parallel rather closely those of other observers who have used heat therapy. A large percentage of patients obtain temporary relief, only a small number of whom maintain this improvement for a year.

I have administered typhoid vaccine intravenously for twenty years in the treatment of this disease. About 40 per cent of the patients are entirely relieved from pain and tenderness after they have received from three to five injections, given every other day. Within a month 50 per cent have a return of the disease, because, I surmise, of incomplete destruction of the infective agent. Most of the remainder of the group have a return of the disease after several months or perhaps a year. A few of the patients have not had a recurrence during the five to ten years that have elapsed since treatment. The earlier in the disease the treatment is instituted, the better the results.

Apparently heat and foreign protein therapy are responsible for recovery from the infection in a small percentage of those treated. The later recurrence of the disease should not be used as an argument against the value of this form of therapy. A spontaneous remission is usually followed by recurrence of the disease.

*Focal Infections*—Under the term focal infection is included two types: acute focal infection and symptomless chronic foci. The acute focal infections that are of special interest in rheumatoid arthritis are those of the upper respiratory tract: nasopharyngitis, acute sinusitis, laryngitis and tracheitis. The chronic foci of special interest are those in the tonsils, teeth and sinuses. There is a small group of physicians who stress the intestinal tract as the source of infection. In recent years little has been written on the gallbladder and the prostate as

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21 Short, C. L., and Bauer, W. Treatment of Rheumatoid Arthritis with Fever Induced by Diathermy, *J. A. M. A.* **104** 2165 (June 15) 1935.

sources of chronic foci. More attention is directed toward the teeth, the tonsils and the sinuses.

Of these two types of infection, chronic foci have been considered the more important. At least these are the foci that are first attacked. Steindler<sup>22</sup> examined 3,000 patients with rheumatoid arthritis and 1,335 with osteo-arthritis for evidence of chronic foci of infection in the tonsils, teeth, sinuses, intestinal tract, prostate and adnexae. Of the 522 cases of rheumatoid arthritis in which foci were found, the tonsils were infected in 55 per cent, the sinuses in 45 per cent, the teeth in 16.5 per cent, the intestinal tract in 1.5 per cent and the prostate and adnexae in 7 per cent. Of the 240 cases of osteo-arthritis in which foci were found, the tonsils were infected in 47 per cent, the sinuses in 56 per cent, the teeth in 28 per cent, the intestinal tract in 7 per cent, and the prostate and adnexae in 5.3 per cent. Steindler reported lasting improvement after the removal of foci in 35 per cent of patients with rheumatoid arthritis and in 20 per cent with osteo-arthritis. The value of these figures depends on how the information was obtained. Subjective information is of limited value.

It is difficult to evaluate the results of such a study. I believe that physicians will agree that from simple observation the tonsils and teeth of patients with rheumatoid arthritis are not different from those of the routine type of patient who enters a physician's office. The patients with osteo-arthritis in this group might be considered controls, as there is no evidence that the disease is directly due to infection.

The numerous reports of favorable results after the removal of chronic foci of infection are not convincing. As a rule, this was not the only method of treatment employed but was combined with hydrotherapy, physical therapy or some other method of treatment. There is little evidence in the reports that the improvement was confirmed by objective study. A not uncommon method employed in obtaining information from the patients is by letter.

The feelings of patients with rheumatoid arthritis vary from day to day. The improvement in the patient with osteo-arthritis can be explained on the same basis. In both groups the power of suggestion and the psychic influence of surgical intervention should be weighed.

There is considerable evidence that chronic rheumatoid arthritis is due to infection with some type of hemolytic streptococcus, as shown by the agglutination and precipitation tests. There is no evidence that *St. viridans* plays a rôle.

In 1927 Rosenow reported the results of cultures of material from twenty-five granulomas from patients with various diseases. Eighty per cent showed pure growth of nonhemolytic streptococci, 12 per cent

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22 Steindler, A. Proc. Am. Soc. Control Rheumatism, 1934.

showed a mixed growth of streptococci, staphylococci and bacilli, and 8 per cent gave negative results. No mention was made of finding hemolytic streptococci. Lehman<sup>23</sup> made cultures from 167 granulomas. Three were sterile. The others contained various forms of streptococci (many unclassifiable), but no mention was made of the presence of hemolytic streptococci. From a single granuloma he usually noted a pure culture of a single strain of *Str. viridans*, but different strains were present in granulomas from different teeth of the same patient.

In experimental efforts to reproduce the pathologic process of chronic rheumatoid arthritis in rabbits, no one has produced changes even remotely resembling those of that disease. If small doses (1 cc) of vaccine are used no changes in the joint are produced, if large doses (and these are often of ridiculous size) are used changes in the joints may be produced, but they have the character of suppurative arthritis. Even to obtain these changes young rabbits must be used. It can be said definitely that there is no experimental evidence that chronic foci of infection are responsible for rheumatoid arthritis.

There is abundant evidence that the removal of tonsils does not prevent acute recurrent rheumatic fever. Davis<sup>24</sup> noted that of 185 patients with a history of rheumatic fever who had their tonsils removed 77 per cent had recurrences of the disease. A statistical report by Kaiser was referred to by Davis. Of 20,000 school children who had had their tonsils removed, 8 per cent had rheumatic fever, of 28,000 children who had not had their tonsils removed, 10 per cent had rheumatic fever.

Finland, Roby and Herman<sup>25</sup> reported on 654 consecutive cases of acute rheumatic fever and noted that removal of the tonsils did not have any effect on recurrences. In this group 114 patients had had their tonsils removed previous to the first attack of rheumatism. Of the entire group, 43 per cent reported sore throat preceding the attack. Removal of the tonsils did not prevent sore throat.

A conservative statement can be made at the present time that there is no convincing evidence that the infective agent in rheumatoid arthritis is derived from chronic foci, and, consequently, it is probable that the foci are not responsible for recurrences. It is especially unfortunate that the removal of chronic foci is considered as the first and major treatment of the disease. This procedure is responsible for the loss of much valuable time which might be utilized more profitably in other procedures.

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23 Lehman, W. Verhandl. d. deutsch. Gesellsch. f. inn. Med., 1930, p. 482.

24 Davis, J. S., Jr. Am. J. M. Sc. **186**: 180, 1932.

25 Finland, M., Roby, W. H. and Herman, H. Am. Heart J. **8**: 343, 1933.

In a disease that pursues such a variable course it is essential with any method of treatment that treated patients and a control group be observed simultaneously. Such a method is now under way at the Presbyterian Hospital in New York. Foci of infection are removed in one group, and the patients receive the same after-treatment as the controls, in whom infective foci are not treated. Dr. Dawson, who is aiding in the study, believes that in four or five years he and his associates will be able to throw some light on this perplexing question.

What evidence is there that acute infections of the upper respiratory tract are the source of infection in this disease? There is very little positive evidence. It is generally accepted that the onset of acute rheumatic fever is preceded frequently by sore throat. In the region of the nasopharynx there are no protective lymph glands to filter out the infection. The virulence of the micro-organism is probably greater in acute infections, and time is required for the development of immune bodies. In cases of chronic foci the virulence of the germ is probably lessened and the body may have acquired some immunity.

Recurrent attacks of rheumatoid arthritis are frequently preceded by colds in the head. Climate is an important factor in the incidence of rheumatoid arthritis, and there is no evidence that climate affects chronic foci.

*Diet*—Many dietary fads have been recommended for the treatment of the disease. These have been adequately discussed by Bauer<sup>26</sup>. He concluded that the best diet is well balanced, such as that which is usually eaten by intelligent persons in good health. Patients with this disease are usually undernourished and require a full diet. There is no satisfactory evidence that vitamin deficiency plays a rôle.

*Relief from Pain*—Heat applied in any manner often gives considerable relief. Acetylsalicylic acid given in moderate doses frequently repeated often will make the patient more comfortable. When the pain prevents sleep and is not relieved by the aforementioned means  $\frac{1}{2}$  grain (0.03 Gm.) of codeine sulfate alone or combined with a hypnotic may permit the patient to sleep. Acetylsalicylic acid, if administered, should be given to relieve pain, it has no effect on the course of the disease.

Many patients of moderate means go to a sanatorium in order to take baths in what is reported to be water of special value in the treatment of rheumatism. The psychologic effect of such a resort may be of value, but the water has no more value than that in the home bathtubs.

The patient with rheumatoid arthritis of the weight-bearing joints should remain in bed.

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<sup>26</sup> Bauer, W. What Should a Patient with Arthritis Eat? J. A. M. A. 104:1 (Jan 5) 1935.

*Sulfur Therapy*—Cawadias<sup>27</sup> noted that the urine of patients with rheumatoid arthritis contains excessive amounts of sulfur. It was later demonstrated that the nail clippings of patients with this disease contain less sulfur than occurs in the nails of normal persons. This gave rise to the idea that rheumatoid arthritis was due to a deficiency of sulfur, a rather speculative deduction. Cawadias stated that sulfur plays a rôle in the proper nutrition of cartilage. The recent literature contains numerous reports on the curative value of colloidal sulfur administered intramuscularly or intravenously. In none of the reports is mention made of suitable controls having been used or of careful objective study of the reputed improvement. The period of treatment is prolonged, and this gives an opportunity for spontaneous improvement.

*Gold Salt Therapy*—Many papers have appeared recently on this method of treatment. Foerstier<sup>28</sup> reported on 500 cases of rheumatoid arthritis in which treatment consisted of the subcutaneous injection of gold salts. He reported improvement in 50 per cent of the cases in which the condition was in an early stage and in from 20 to 30 per cent of those in which it was in a late stage. The treatment extends over a long period. No controls were used, and such a report is of limited value. Treatment with gold compounds can, and often does, cause serious renal damage.

*Prevention of Deformity and Ankylosis*—The prevention of deformity and ankylosis is just as important as the attempt to destroy the infection. If the infection disappears spontaneously or as a result of treatment and the patient is a permanent cripple he is still an invalid. From the onset of the disease efforts should be directed toward the prevention of deformity. If an orthopedic surgeon is available he should take charge of this phase of the treatment. If this is not possible, the general practitioner or internist in charge should direct his attention to this complication. When the synovium is destroyed and then replaced by connective tissue fixation of the joint, even for a relatively short period, ankylosis will almost certainly follow. It is important that daily gentle slight movement of the joint, adequate to prevent ankylosis, be carried out. In the acute stage of the disease complete rest, with the application of heat and moderate doses of acetylsalicylic acid, may be necessary for a few days before even slight movement can be undertaken. Deformity is due largely to muscle spasm, and experience will enable the physician to anticipate the type of deformity that usually develops. As an illustration, when the wrist is involved, ulnar deviation of the hand is a common type of deformity.

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27 Cawadias, A. Brit M J 2 602 1926

28 Foerstier, J. Lancet 2 646, 1934

In the knee there is a tendency to marked flexion of the leg. Muscle spasm is a physiologic effort to put the joint at rest.

Heat, gentle massage and various forms of physical therapy are helpful. A baker into which the extremity can be placed is a simple and efficient way to apply heat. Light bivalved plaster of paris splints for the purpose of holding the extremity in its normal position can be applied at night or if necessary during the day. These should be removed daily or at most every second day, and the extremity should be moved gently to avoid ankylosis. The patient should be encouraged to make the movement himself. When the fingers are involved the patient should be urged to attempt to make a fist many times a day. It is much easier to prevent deformity than it is to correct it later.

This brief discussion of such an important subject is entirely inadequate. However, the treatment of this complication of rheumatoid arthritis belongs in the domain of the orthopedic surgeon.

*Ganglionectomy*—Ganglionectomy, which a few years ago was advocated to relieve or prevent deformities, has been found to be of limited value. The operation is now restricted to young patients without ankylosis and is of value only when the small articulations are involved.

*The Prevention of Reinfection*—Spontaneous remissions are not infrequent but may be followed later by reinfection and recurrence. There is evidence that fever therapy, in a limited number of cases, is followed immediately by the disappearance of all evidence of infection. Later, often after several months has elapsed, the disease recurs. It is probable that the recurrence is due to reinfection. If this is true, are there any preventive therapeutic measures? If such a patient during a remission would make his home in the tropics at sea-level, it is highly probable that the disease would not recur. As the disease is relatively rare in the states bordering on the Gulf of Mexico and also in the dry region of the Southwest, permanent residence in such a location would lessen the probability of recurrence. Measures to improve the patient's general health and to maintain it at a high level may be of some value.

## News and Comment

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### AMERICAN COLLEGE OF PHYSICIANS

The Twentieth Annual Session of the American College of Physicians will be held in Detroit on March 2 to 6, 1936, at the Book-Cadillac Hotel. The president, Dr. James Alexander Miller, will deliver an address on "The Changing Order in Medicine." Dr. Walter B. Cannon, professor of physiology at Harvard University Medical School, will deliver the annual convocation oration on "The Rôle of Emotion in Disease." About fifty eminent authorities will present papers in the general scientific sessions, and clinics and demonstrations will be conducted at the Harper, Receiving, Henry Ford, Grace, Herman Kiefer and Children's Hospitals.



## Book Reviews

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**The Carotid Sinus and the Cerebral Circulation** By Erik Ask-Upmark  
*Acta psychiatrica et neurologica, Supplement VI Pp 374, Lund, 1935*

Ask-Upmark has approached the problem of the relationship between the carotid sinus and the cerebral circulation from three angles anatomic, experimental and clinical. Following an extensive general introduction, he describes the dissection of the carotid sinus in twenty-seven species of mammals, reptiles, amphibia and birds. The sinus is located at the origin of the internal carotid artery or its homologs. In the absence of the internal carotid artery the site is the base of the occipital artery. The sinus is innervated chiefly by the glossopharyngeal, partially by the vagus and the sympathetic, and rarely by the hypoglossal, nerves. The glossopharyngeal nerve is especially important, judging from the morphologic and physiologic evidence presented. Embryologically, this is to be expected, since the sinus is probably derived from the arterial structures of the third branchial arch, which lies in the domain of the ninth nerve. It is regrettable that microscopic studies were not made on the sinus and its innervation, the Bielschowsky technic would have been applicable to the specimens, however long they may have been fixed in solution of formaldehyde. No neurocytologic attempts were made to determine the central source of the fibers innervating the sinus.

Incorporated in the section on anatomy is an interesting, albeit lengthy and questionably relevant, discussion of the rete mirabile caroticum. Observations seem to show that this network, which is homologous to the pseudobranch of certain fishes, reaches a development in different species that varies inversely with the importance of the internal carotid artery as the chief source of cerebral blood.

The comparatively brief section on experimental work deals with direct observation of the pial vessels during stimulation of the sinus. Changes in the diameter of the vessels were variable, vasoconstriction being more common than vasodilatation. The author interprets constriction as a passive response to decrease in the systemic blood pressure. Active dilatation, when present, is dismissed as unimportant. In addition to a passive relationship between the cerebral and systemic vascular systems, he believes that there may be an active vasomotor reflex from the sinus. The path of such a reflex is obscure. On the whole, the paucity and variability of the experiments render the observations inconclusive.

Ask-Upmark attempts to correlate his observations on the sinus with various clinical conditions. In cases of syncope, which are clearly related to irritation of the carotid sinus, he believes that the cerebral changes are secondary to systemic variations. The work of Weiss and Baker, who found no similar relationship in some of their cases, is unfairly criticized on the basis that a transitory fall of blood pressure might have been overlooked. The same objection might validly be made to Ask-Upmark's experiments, since kymographic records were not made. The author considers the possibility of a relationship between the carotid sinus and epilepsy, cerebral vascular accidents and postural hypertension.

Two points of practical importance are brought out. In cases of tumor of the carotid body and in operations in the neck, sudden vascular phenomena may be related to injury to the sinus. Furthermore, Ask-Upmark has observed that during operative intervention in the cerebellopontile angle a dramatic fall in blood pressure may not infrequently occur on cutting or pulling on the ninth nerve.

In reviewing the records of four hundred and eighty-six verified tumors of the brain, operated on by Cushing, the author found that a low systolic blood pressure was a common occurrence (in 20 per cent of the cases), especially in instances of supratentorial lesion, not infrequently the reverse was found in cases of infratentorial tumor. He assumes that the presence of hypotension may be due to an involvement of the hypothalamico-hypophyseal apparatus. In attempting to link up

the hypothalamus with the carotid sinus, however, his enthusiasm has carried him beyond the known anatomic and physiologic evidence. Hypertension associated with tumors of the posterior fossa is treated conservatively, being explained by Cushing's theory of anemia of the vasomotor centra.

The work as a whole represents a great amount of personal industry during a relatively brief period and on this score is a tribute to the author's resourcefulness and ability. The investigation on the comparative gross anatomy is a distinct introductory contribution, and the compilation of an extensive bibliography will be a boon to workers in the field of cerebral circulation. The book, however, is far too lengthy for its contents and suffers greatly from poor editing, frequent repetitions and numerous contradictions. Individual publication of the separate sections would have been well advised. As it is, Ask-Upmark's attempt to mold his theories, as well as his observations, into a unified presentation against the background of the literature has resulted in a monograph which, viewed in toto, represents a superficial and rather unwieldy analysis of an intricate problem.

**Child Psychiatry** By Leo Kanner, M.D., associate professor of Psychiatry, the Johns Hopkins University. With prefaces by Adolph Meyer, M.D., LL.D., Henry Phipps Professor of Psychiatry, the Johns Hopkins University, and Edwards A. Park, M.D., Professor of Pediatrics, the Johns Hopkins University. Cloth. Price, \$6. Pp. 527. Springfield, Ill. Charles C. Thomas, Publisher, 1935.

In his introduction Kanner calls this "the first textbook of child psychiatry in the English language" and adds that it "is offered as an attempt to cover the entire field of children's personality disorders on a broad, objective, unbiased and practical basis." The first hundred and forty pages are devoted to basic principles, methods of examination and diagnosis and fundamental considerations regarding psychiatric treatment of the child. The remainder of the book deals with specific psychiatric disorders, many of which are, with doubtful propriety, renamed according to the peculiar nomenclature of the Meyerian school. These have been divided into personality difficulties (1) associated with physical illness, (2) expressing themselves as involuntary "part-dysfunctions" and (3) expressing themselves clearly as "whole-dysfunctions" of the individual.

Concerning the general organization of the subject matter, little criticism need be made. The separation of part-dysfunctions from whole-dysfunctions is, however, unjustifiable. For example, it is difficult to see the logic in classifying globus hystericus, aerophagia and psychogenic vomiting as part-dysfunctions merely because they are manifested in the gastro-intestinal tract, while stuttering is placed in the group of whole-dysfunctions.

Kanner is a representative of the "psychobiologic" school of Adolph Meyer. In a short chapter on the principles of psychobiology and psychopathology he outlines the philosophic attitude of this school to the broad problem of personality disorders. The psychobiologist has a formula by which he regards the individual as a biologic unit reacting to the environment as an integrated functioning whole. Kanner is under the impression that this formula enables him to solve, or at least to ignore, the age-old enigma of mind and body, an enigma which has troubled the student of human behavior for centuries. He states "The very moment that we recognize behavior, both overt and implicit, as a function of the total organism, the confusing contrast between body and mind, between physical and mental, no longer exists, or need disturb anyone" (p. 14). This is, of course, a complete non sequitur, and the psychobiologist who uses such an argument deceives no one but himself. That the individual functions as an integrated whole, which is more than the sum of its parts is a truism, which, however, fails to explain the respective rôles and importance of mind and body in the individual.

The psychobiologist calls himself a "pluralist," which is to say that he will accept any "explanation" of a behavior abnormality which investigation brings to

light. He sees good in all systems of psychiatric thought, but gives his allegiance to none. Thus the most diverse points of view are recognized, from those of Watson to those of Freud. Aside from philosophic objections, such a "pluralism" leads rapidly to opportunism and finally to superficiality. Unless one seeks for fundamentals one is perforce superficial, and such superficiality is sadly in evidence in this book. Many examples might be given. For example, in discussing disorders of speech, Kanner states that stuttering began in one patient "after some firecrackers exploded near her, in a boy who was threatened that his ear will be cut off, in a boy whose father also stuttered, and whose own speech disorder began when he and his parents were told that he had tuberculosis, in a boy who began to stutter when he was frightened by a dog, in a youngster whose speech trouble followed immediately a fall down stairs, in a boy whose perfectly normal speech was changed to stuttering on the morning after his first public recitation before a large audience. Interference with the use of the hand of preference was reported in a considerable number of stutterers." All these statements may be true, but they are so superficial as to deceive no one. There is no attempt by the author to understand the mechanism of stuttering, to study its psychopathology or, if one prefers, its physiopathology. There is simply a listing of insignificant antecedents, with a complete ignoring of fundamental mechanisms.

This superficiality is a fatal defect throughout the whole book. In the discussion of the "minor psychoses" (psychoneuroses) one searches in vain for any reference to psychopathology. There is likewise no attempt to deal with abnormal physiology in these states. Regarding hysteria Kanner has no theories of his own but culls from various conflicting hypotheses and adds, "There is some truth in all these theories." The discussion of the psychoses is limited to description. One is left without any psychopathologic interpretation to aid in understanding night terrors, somnambulism, pathologic lying, kleptomania and sadism and is asked to believe that these abnormalities result in a more or less haphazard fashion from such vague factors as "physical, constitutional, emotional, intellectual or environmental" difficulties. In the discussion of the behavior disturbances in chronic encephalitis there is no attempt to understand how encephalitis produces the disturbances, and the same is true regarding the mental states following trauma to the head.

The careful study of children will eventually make great contributions to the psychiatry of the future, since it is in childhood that the origins of behavior disturbances are to be found. Psychotherapy must be applied early in life to achieve its greatest results. It is unfortunate that this "first textbook of child psychiatry in the English language" should fall so far short of making fundamental contributions in this tremendously important field.

**The Kidney in Health and Disease.** In Contributions by Eminent Authorities. Edited by Hilding Berglund, M.D., Stockholm, Sweden, formerly chief of the department of medicine at the University of Minnesota, and Grace Medes, Ph.D., research biochemist in the Lankenau Hospital Research Institute, Philadelphia. With the collaboration of G. Carl Huber, M.D., University of Michigan, Warfield T. Longcope, M.D., Johns Hopkins University, and Alfred N. Richards, Ph.D., M.D., University of Pennsylvania. Cloth. Price, \$10 net. Pp. 774, with 163 illustrations. Philadelphia: Lea & Febiger, 1935.

This volume, attractively gotten up, "is the outgrowth of a symposium on the structure and function of the kidney in health and disease which took place in Minneapolis during the summer of 1930." In putting these papers into book form an effort has evidently been made to arrange the material so as to cover the subject in a more or less systematic manner. The first section on anatomy and physiology, including articles by Huber, Richards, Marshall, Rehberg and others, is satisfactory. In the subsequent parts of the book one has, on the contrary, a feeling of spottiness, as though one were reading a series of more or less

unrelated articles in a journal rather than a monograph. Even though many of these articles are excellent, one wonders whether the substance could not have been boiled down to a more homogeneous concentrate. First and last, the book covers rather well modern ideas about the function of the kidney and disease—probably better than any other available single volume.

**Diseases of the Endocrine Glands** By Hermann Zondek. Third edition. Translated by Carl Prausnitz. Price, \$11. Pp 492, with 168 illustrations. Baltimore: William Wood & Company, 1935.

Coming from the pen of an eminent investigator in the field of endocrinology, this book could hardly fail to be of great interest. It is, in fact, a scholarly work dealing with the subject from the fundamentals up. The clinical descriptions are excellent and the illustrations well chosen. In view of all this, one is disappointed by the inadequate way in which certain phases are handled, especially therapy. The question of the use of iodine in cases of exophthalmic goiter is dealt with vaguely, and one is aghast at the directions given for the use of thyroid substance in myxedema. Even more surprising is the suggestion that parathormone be used in osteitis fibrosa cystica, and that in the discussion of the treatment of Addison's disease the use of sodium chloride is passed by with a casual sentence. The discussion of obesity is so confused as to be useless, and emphasis is placed on all sorts of drug therapy as against diet.

While the book is of interest to the advanced student of endocrine disease, one would doubt its value to the average physician seeking sound procedures in dealing with these disorders.

**Kliniske studier over den digestive duodenalsaftsekretion** By Tage Christiansen. Paper. Pp 229, with 17 figures, 46 tables and 112 protocols. Copenhagen: Levin & Munksgaard, 1933.

This doctor's dissertation contributes important data on two questions. The first is whether the individual glands (the liver, the pancreas and the duodenal glands) which pour their secretion into the duodenum are capable of adapting the nature of their secretion to the nature of the food to be digested, and the second is whether normal gastric digestion is a necessary prerequisite for normal duodenal digestion. In studying the former question Christiansen took a series of normal human subjects and by means of an Einhorn tube introduced into their duodenum chyme obtained by aspiration from the stomachs of other normal subjects. The donors had masticated and swallowed meals consisting of starch, veal or 16 per cent cream, according to whether carbohydrate, protein or fat was to be studied. This avoided many of the objections to experiments on animals and to observations on human patients with traumatic or surgical fistulas and enabled the author to control both the volume and the composition of the chyme reaching the duodenum. The resulting duodenal juice was aspirated continuously over thirty minute periods and studied for volume, color, trypsin, diastase, lipase and bilirubin. From the results of eighty successful experiments Christiansen concludes that two types of response can occur separately or in combination: an enzyme-rich secretion evoked by the natural secretagogues in the food and a defensive secretion evoked by the hydrochloric acid in the chyme from the stomach. He believes that the importance of hydrochloric acid in rousing the tributaries of the duodenum to the production of digestive juice has been overrated. Hence his interest in the patient with achylia gastrica. A series of thirty-two experiments on achylic patients receiving a variety of chymes, including chyme aspirated from the stomachs of other achylic patients, convinced him that the effluent from an achylic stomach contains substances which are strongly stimulating to the pancreas, that the achylic patient's pancreas responds normally to these substances and that achylia gastrica need not be accompanied by pancreatic achylia or by any other insufficiency of duodenal digestion.

**Die ansteckenden Krankheiten** Edited by Dr Max Gundel Price, unbound, 35 marks Pp 641, with numerous illustrations and tables Leipzig Georg Thieme, 1935

This is a German compendium on infectious diseases written by twenty-one different authors and assembled under the editorship of Gundel of the Koch Institute in Berlin It is a most interesting compilation

The various infectious diseases are discussed in considerable detail from the points of view of their etiology, clinical manifestations and particularly from the aspects of their epidemiology, preventability and therapy Present conceptions regarding vaccination, the use of various antisera and transfusions are well described Each chapter ends with a number of references to the current literature

The book is thoroughly German in character and gives comparatively little consideration to work on infectious diseases by other than German authors Without doubt, however, it is an important reference book It is well set up and clearly written On the whole, it deserves recognition in this country and should fill competently a niche in all American medical libraries

**Therapie der Herzkrankheiten** By Prof N von Jagic and Dr Ernst Flaum Price, 10 50 marks Pp 331, with 13 illustrations Berlin Urban and Schwarzenberg, 1935

This book emanates from the Second Medical University Clinic in Vienna One of the authors is chief of this clinic, and the other has done much clinical and pharmacologic work in its station for diseases of the heart The volume is designed to describe the manner in which heart disease is treated there and to contain as much practical information as possible

The contents follow a logical arrangement First is discussed the treatment of heart disease in general, then follow chapters dealing with the management of individual phases of heart disease, such as congestive failure, valvular disease and pericarditis One of the engaging features of the book is that no time is spent in reviewing the literature Von Jagic states in the preface that there are already many reliable sources for this information, he wishes to express his own views on the treatment of heart disease, founded on the experience of his own clinic There is a certain amount of repetition, so that parts may seem unnecessarily redundant On the other hand, there are detailed descriptions of many tricks of the trade which are worth knowing how bowels are managed in that particular clinic, how sleep and rest are induced, how patients with cardiac disease are fed and how digitalis, strophanthin and the various diuretics are employed

On the whole, the book is interesting It will be well thought of in Vienna and by the practitioners there for whose benefit it was put together Internists in America will be glad to refer to it, for it gives a clear account of how diseases of the heart are being cared for at the present in a thoroughly representative and highly respected foreign institution

## PHARMACOLOGIC AND THERAPEUTIC PROPERTIES OF CRYSTALLINE VITAMIN C (CEVITAMIC ACID)

WITH ESPECIAL REFERENCE TO ITS EFFECTS ON THE  
CAPILLARY FRAGILITY

IRVING S WRIGHT, M D  
AND  
ALFRED LILIENFELD, M D  
NEW YORK

The isolation of hexuronic acid from cabbages, orange juice and adrienal cortex by Szent-Gyorgyi<sup>1</sup> in 1928 opened a new field for investigation, which culminated in 1932 with its identification as crystalline vitamin C, now termed cevitamic acid<sup>2</sup>

This substance is an odorless, white or yellowish-white crystalline powder, with a melting point of from 189 to 192 C. An outline of its properties follows

**Formula** The acid titration corresponds with the formula  $C_6H_8O_6$ <sup>3</sup>

**Solubility** It is freely soluble in water and also soluble in acetone, acetic ether and propyl alcohol, and insoluble in ethyl ether and purified petroleum benzene<sup>4</sup>

**Stability** It oxidizes on exposure to air and light. In an inert atmosphere it is quite stable to moderate heat, even in alkaline solution<sup>5</sup>. It is decomposed when heated above 185 C<sup>3a</sup>

This study was aided by a grant from the Josiah Macy Jr. Foundation

Read before the Section of Medicine, New York Academy of Medicine, April 16, 1935

From the Second Medical Division, Bellevue Hospital (Cornell University Medical College), Henry J. Spencer, M.D., director, and the Department of Medicine, New York Post-Graduate Medical School and Hospital (Columbia University), Herman O. Mosenthal, M.D., director

1 Szent-Gyorgyi, A. Biochem J **22** 1387, 1928, Nature, London **129** 576, 1932

2 (a) Tillmans, J., Hirsch, P., and Hirsch, W. Ztschr f. Untersuch d. Lebensmitt **63** 1, 1932. (b) Svirbly, J. L., and Szent-Gyorgyi, A. Biol J **26** 865, 1932. (c) Szent-Gyorgyi, A. Deutsche med. Wchnschr **22** 852, 1932. (d) Zilva, S. S. Nature, London **129** 3269, 1932. (e) Waugh, W. A., and King, C. G. J. Biol. Chem. **97** 325, 1932.

3 (a) Waugh, W. A. J. Chem. Educ. **11** 69 (Feb.) 1934. (b) Birch, T. W., and Harris, L. J. Biochem J **27** 595, 1933.

4 Sipple, H. L., Grettie, D. P., Svirbly, J. L., and King, C. G. J. Biol. Chem. **94** 483, 1931-1932. Matsuoka, Tomiji. J. Agric. Chem. Soc. Japan **9** 1130, 1933.

5 Herbert, R. W., and others. J. Chem. Soc., Sept. 1933, p. 1270.

**Reducing power** It has a high reducing power. This reducing power is the more remarkable since the oxidation of the acid is reversible. It is by this reversible oxidizability that the substance probably exerts its biologic activity. It is oxidized and reduced alternately, giving off and taking up two atoms of hydrogen, thus acting as a hydrogen carrier between different parts of its oxidation system.<sup>6</sup>

**Salts formed** Precipitation as lead salt from an alcohol or water solution is consistent with regard to activity and properties.<sup>10</sup>

**Diffusion** The active factor of vitamin C diffuses rapidly through a collodion membrane.<sup>7</sup>

**Effect of light** The vitamin C (reducing substance) in milk is apparently sensitive to visible light.<sup>8</sup>

**Color reaction** A slightly alkaline solution acquires, on standing with ferrous sulfate, a dark violet color.<sup>9</sup>

**Absorption spectrum** In methyl alcohol and in aqueous solution (20 mg per liter) an intense band is found at from 200 to 265 microns. In ethyl alcohol and also in acidified aqueous solutions the band occurs at 245 microns.

**Optical rotation** (with a 10 per cent solution)<sup>10</sup>

$$[\alpha]_{20/D} = 24 \text{ to } 25$$

$$[\alpha]_{22/D} = 23$$

$$[\alpha]_{24/D} = 21.01$$

**Pigmentation** Cevitamic acid prevents the formation of pigment in the tissue sections.<sup>9a</sup>

**Potentiometric studies** In cevitamic acid the  $\text{—CHOH—}$  group between the two CO groups rapidly gives up 2H at a potential level corresponding approximately to the value rH-17.<sup>11</sup>

**Chemical determination** The method described by Harris and Ray is based on modifications in the use of Tillman's indicator, sodium 2,6-di-chlorophenol indophenol. The essential features are a preliminary extraction process with tri-chloroacetic acid, followed by titration in acid solution. These conditions are necessary in order to rule out interference by other reducing substances present in many animal tissues, notably glutathione, which would otherwise render the test of little significance.<sup>12</sup>

Since the original work, this substance has been obtained also from adrenal medulla, corpus luteum, lemon juice, paprika, green pepper,

6 Szent-Gyorgyi, A. *Nature*, London **131** 225 (Feb 18) 1933. Haworth, W. N. *Chem & Industry* **52** 482 (June 9) 1933.

7 McKinnis, R. B., and King, C. G. *J Biol Chem* **87** 615, 1930.

8 Kon, S. K. *Nature*, London **132** 64 (July 8) 1933. Mattick, A. T. R., and Kon, S. K. *ibid*, p 446.

9 Schroeder, H. (a) *Klin Wchnschr* **13** 553, 1934, (b) *Bull Soc chim biol* **4** 83, 1922. Bessonov, N., and Delire, A. *Compt rend Acad d sc* **196** 2036 (June 26) 1933.

10 Lowry, T. M., and Pearman, S. A. *J Chem Soc*, Nov 1933, p 1444. Waugh and King<sup>2e</sup> Waugh<sup>3a</sup>.

11 Wurmser, Rene, and de Loureiro, J. A. *Compt rend Soc de biol* **113** 543, 1933. Georgescu, I. *J de chim phys* **29** 217, 1932. Green, David E. *Biochem J* **27** 1044, 1933. Waugh (footnotes 2e and 3a).

12 Harris, L. J., and Ray, S. N. *Biochem J* **27** 303, 1933.

gladiolus, iris, skunk cabbage (*Symplocarpus foetidus*), parsley, watercress and other sources

The formula ( $C_6H_8O_6$ ) was accepted, and it was found that less than 1 mg of this substance a day was enough to keep a guinea-pig free from scurvy. The structural formula, however, has been a matter of considerable study and discussion, principally by Cox and Hirst,<sup>13</sup> Karrer<sup>14</sup> and Micheel.<sup>15</sup> It has since been synthesized.<sup>16</sup>

One of the first questions to arise was whether the antiscorbutic effects produced by the use of cevitamic acid were due to the inherent properties of a pure substance or whether they came from an attached impurity. The point was made that vitamin C could perhaps be present only as an impurity of cevitamic acid, since the protective dose is so many times greater than that of vitamin A (Ratte), B (Taube) and D (Ratte). Since it may be pointed out that vitamin C is much more abundant in nature, providing in the natural diet a supply which is easily adequate, such a conclusion appears unwarranted.

Rygh,<sup>17</sup> at the beginning of 1932, expressed the belief that he had isolated vitamin C from orange juice, and he identified it as methylnornarcotine, which he claimed was an antiscorbutic agent for guinea-pigs. Dalmer and Moll,<sup>18</sup> Bruggeman<sup>19</sup> and Grant, Smith and Zilva<sup>20</sup> were unable to confirm this work. Rygh published further experiments<sup>21</sup> in which he claimed to have demonstrated that while methylnornarcotine prevented scurvy in guinea-pigs it did not enable the animals to live. The simultaneous administration of glycuronic acid, however, in daily doses of 0.5 mg maintained life. He assumed, on the basis of this experiment on animals, that the guinea-pig fed a diet free from vitamin C is not able to form the glycuronic acid necessary for the maintenance of life and believed that he could draw the further conclusion from his work that hexuronic acid, found by Szent-Gyorgyi, was antiscorbutic only by virtue of traces of methylnornarcotine which it contained. In the light of much recent work, this does not appear to be correct. The antiscorbutic effect is produced even in the most carefully purified preparations of cevitamic acid. Carefully fractioned crystalli-

13 Cox, E. G., Hirst, E. L., and Reynolds, R. J. W. *Nature*, London **130** 888, 1932, *Chem. & Industry* **52** 221, 1933.

14 Karrer, P. *Biochem. Ztschr.* **4** 258, 1933, *Helvet. chim. acta* **16** 302, 1933.

15 Micheel, F., and Kraft, K. *Nature*, London **131** 274, 1933, *Ztschr. f. physiol. Chem.* **216** 233, 1933.

16 Reichstein, T., Grüssner, A., and Oppenauer, R. *Helvet. chim. acta* **16** 561, 1933.

17 Rygh, O. *Ztschr. f. physiol. Chem.* **204** 105, 1932.

18 Dalmer, O., and Moll, T. *Ztschr. f. physiol. Chem.* **209** 4 and 211, 1932.

19 Bruggeman, J. *Ztschr. f. physiol. Chem.* **211** 3 and 231, 1932.

20 Grant, R. I., Smith, S., and Zilva, S. S. *Biochem. J.* **26** 1628, 1932.

21 Rygh, O., and Rygh, A. *Ztschr. f. physiol. Chem.* **211** 275, 1932.

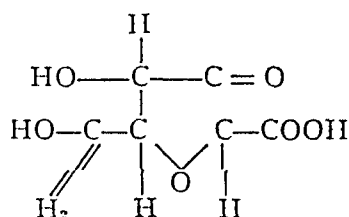


zation of cevitamic acid (Karrer<sup>14</sup>) has shown that it is not possible to get crystals of varying potency. Szent-Gyorgyi further has obtained, by purification through crystallization, mono-acetone cevitamic acid, which has been found by some workers to have only slightly antiscorbutic potency. After splitting off the acetone fraction the cevitamic acid exhibited its unaltered potency.

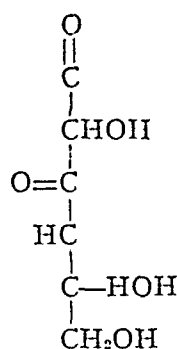
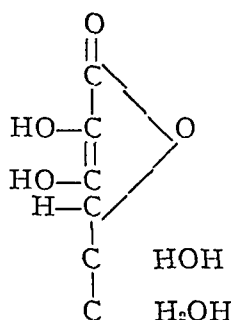
Many investigators<sup>22</sup> have agreed that hexuronic acid has been found completely free from nitrogen. Various other authors<sup>23</sup> have reported that methylornithine together with glycuronic acid is ineffective as an antiscorbutic agent in guinea-pigs. Westin,<sup>24</sup> who examined histologically the animals of Rygh, could discover, according to the tooth method, no evidence of an effect of this combination on the scorbutic appearance of the tooth. Dalmer and Moll<sup>22b</sup> reported that guinea-pigs treated by this method died at the same time as untreated controls and with equally severe scorbutic manifestations.

It would, therefore, appear that at present the weight of evidence is decidedly against the contentions of Rygh in this regard.

Several structural formulas, including the following one suggested by F. Micheel,<sup>25</sup> with what seems to be good substantiation, have been presented.



The formula on the left is believed by Major<sup>26</sup> to be the correct one. An isomer of this is shown on the right.



22 (a) Tillmans, J., and Hirsch, P. *Biochem Ztschr* **250** 312, 1932. (b) Dalmer, O., and Moll, T. *E. Merck's Jahresb.*, 1932, p. 19. Szent-Gyorgyi<sup>1</sup> Waugh<sup>2e</sup>

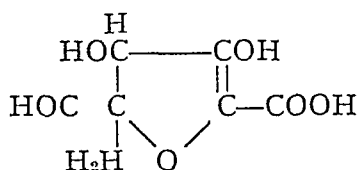
23 Widmark, E. M., and Glinstedt, G. *Ztschr f. physiol. Chem.* **215** 147, 1933. Reschke, J. *ibid.*, p. 164. Dann, W. J. *Nature*, London **131** 24, 1933.

24 Westin, G. *Ztschr f. Vitaminforsch.* **2** 1, 1933.

25 Micheel, F. *E. Merck's Jahresb.*, 1932, p. 4. Micheel and Kraft<sup>15</sup>

26 Major, R. Personal communication to the authors.

The following isomer has also been suggested, but we do not believe that the corresponding chemical has actually been made <sup>25</sup>



Biologic tests of the antiscorbutic effect of cevitamic acid have led to different conclusions, depending on the several methods used, the difference in the use of the same method, the difference in laboratory conditions, the difference in the potency of citrus fruit juice used, variations in animals used and other factors. Svirbly and Szent-Gyorgyi <sup>26</sup> found that 0.5 mg of cevitamic acid corresponded to 1.5 cc of lemon juice. Birch and his co-workers, <sup>27</sup> using the tooth method, determined that 0.6 mg of cevitamic acid has the effectiveness of 1 cc of orange juice. On the other hand, Key and Elphick <sup>28</sup> found that orange juice and lemon juice were equally effective, according to the tooth method. In consideration of the purity of crystalline vitamin C, this seeming paradox must rest with the differences in method, as mentioned previously.

Reports of clinical experience with the use of cevitamic acid have thus far been limited to isolated studies. As is usually the case with a new form of treatment, it has been used in a great variety of conditions. Some of this work has been poorly controlled, and conclusions have been drawn from insufficient evidence, for example, the cessation of bleeding occurring in a single instance in any of the hemorrhagic diseases. This is recognized to be often irregular and capricious. Conclusions founded on such phenomena appear unwarranted. When, however, the results of study of individual cases or of small groups are coordinated and reviewed, such investigations may be of great value.

At a conference on vitamin C held at Darmstadt on April 14, 1934, <sup>29</sup> Professor Stepp of Breslau reported certain effects of vitamin C on various metabolic processes. Following intravenous injections of large amounts of the vitamin, no change was found in the sugar, cholesterol, calcium or phosphorus content of the blood. After several days' administration, a slight increase in the carbon-nitrogen quotient in the urine was found. He reported that injections of 100 mg of cevitamic acid each day for several days resulted in a definite increase in the amount

<sup>27</sup> Birch, T. W., Harris, L. S., and Ray, S. N. *Nature*, London **131** 273 1933.

<sup>28</sup> Key, K. M., and Elphick, G. K. *Biochem. J.* **25** 888, 1931.

<sup>29</sup> Unpublished minutes of Conference on Vitamin C, Darmstadt, April 14 1934.

of albumin, which resulted in alteration of the rate of sedimentation of the blood corpuscles. He reported the case of a patient with purpura rheumatica who showed no improvement under any other form of treatment and in whom he was able to bring about a striking disappearance of the tendency to hemorrhage by the intravenous administration of large doses of cevitamic acid. It was reported, also, that Dr. Stalte of the children's clinic in Breslau confirmed these findings in children with Schonlein-Henoch's disease and also in cases of true "morbus maculosus of Werlhof," which was "markedly influenced" by vitamin C although he did not define what he meant by that.

A variety of additional conditions was reported at this conference as having been influenced favorably by the use of cevitamic acid, e. g., scurvy in childhood, dysentery, leukemia, peritonitis, diphtheria, "hemorrhagic nephritis," acute infections of the respiratory tract, pyuria in childhood (ten cases with nine cures), ununited fractures and certain forms of pigmentation of the skin.<sup>30</sup> It should be stated, however, that these reports were not completed studies but rather informal preliminary observations on the part of a group of workers from throughout Germany. It was fully realized that many of these observations might not be substantiated by further experience.

Professor Gabbe, of Bremen, reported at the same conference a method which permits the determination of the presence of vitamin C in the blood. With this method, he found the normal vitamin C content to be between 0.7 and 1.2 mg. per hundred cubic centimeters of blood. These values rise or fall from 30 to 50 per cent with a higher or lower content of vitamin C in the food. Abnormally low findings were found not only in persons maintained on a diet poor in vitamin C but, in spite of plentiful addition of vitamin C, in persons suffering from severe infections which had lasted for several weeks, e. g., from 0.15 to 0.25 mg. per hundred cubic centimeters in cases of sepsis and typhoid. He felt that these findings indicated a greater metabolic use of vitamins in patients suffering from infection. In patients with carcinoma, values corresponding to the state of nutrition were found in the blood.

Numerous cures of infantile scurvy by the use of cevitamic acid were reported during 1934. Wentzler<sup>31</sup> reported a case in a 6 month old boy in whom signs and symptoms showed a favorable change in six days and who was entirely restored to normal in twenty-one days. The daily dose used was 50 mg. dissolved in the food and taken by mouth. Neumann<sup>32</sup> reported its use in the treatment of a 10 month old child with frank scurvy (Moeller-Bailow's disease). Although there

<sup>30</sup> Morawitz, P. *Klin. Wchnschr.* **13** 324, 1934. Schroeder, H. *Ann. de E. Merck*, 1934, pt. 2, p. 118.

<sup>31</sup> Wentzler, E. *Monatschr. f. Kinderh.* **59** 451, 1934.

<sup>32</sup> Neumann, U. *Deutsche med. Wchnschr.* **81** 1204 (Aug. 10) 1934.

was no other source of vitamin C in the diet, the patient, taking each day 60 mg orally, showed definite improvement in two days and was considered cured in twelve days, with a gain of 550 Gm in weight. Brugsch<sup>33</sup> also reported its use in a child 13 months old, with clinical and roentgenographic evidence of scurvy, which was cleared up in three weeks with a dose of 30 mg a day. He mentioned a similar study by Parsons and Svensgaard. An important factor in these reports is the apparent tolerance of these young infants to cevitamic acid taken by mouth. Kramer<sup>34</sup> showed in 1933 that daily doses of from 20 to 50 mg for several weeks were well tolerated by infants, including premature infants. In investigating the tolerance to cevitamic acid,<sup>29</sup> it has been found that mice showed no disturbances when given as much as 50 mg of cevitamic acid a day for twelve weeks. Guinea-pigs tolerated one hundred times the protective dose for five weeks without change.

Boger and Schroeder,<sup>35</sup> after observing the favorable effect of cevitamic acid, parenterally administered, on capillary hemorrhages of C avitaminosis origin, were encouraged to try its use in a variety of other hemorhagic conditions. They reported first a case of Schonlein-Henoch's purpura, in which they observed a rapid disappearance of the phenomena of increased capillary fragility by the intravenous administration of 100 mg daily. This patient's condition had not been influenced by the previous use of vitamin C by mouth. This phenomenon will be discussed later. The second patient whom Boger and Schroeder discussed was a man with hemophilia, who had severe intestinal hemorrhages. After the daily administration of 150 mg of cevitamic acid intravenously for a few days the bleeding ceased. They did not point out that bleeding frequently stops in patients with hemophilia without any therapy. The third case in this series was that of a man aged 60, with acute thrombocytopenic purpura. He had bleeding from the mucous membranes and subcutaneously and very bloody urine and tarry stools. The patient was acutely ill. After receiving 150 mg of cevitamic acid intravenously for four days, the bleeding ceased and did not recur. The significant findings in the blood were more striking. When the patient was first seen, the platelets were too few to count. Curiously, the bleeding ceased two days before the platelets became plentiful enough to count. There was thereafter a steady increase in number until, after one month of therapy with cevitamic acid (100 mg daily), the count reached 304,000. During the same time the bleeding time decreased from twelve to one and a half minutes. This case emphasizes a point to be stressed later, namely, that the number of platelets

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33 Brugsch, H. *Deutsche med Wchnschr* **81** 1202 (Aug 10) 1934

34 Kramer, E. *Deutsche med Wchnschr* **59** 1428 (Sept 15) 1933

35 Boger, A., and Schroeder, H. *Munchen med Wchnschr* **81** 1335 (Aug 24) 1934

is not the determining factor per se of the clinical course of thrombocytopenic purpura. It is frequently noted that immediately after splenectomy the bleeding stops, although the platelet count does not increase and may even decrease. These authors concluded that it is extremely probable that vitamin C acts on the vessels and that obviously an alteration of the permeability of the walls of the vessels plays an important part in the occurrence of hemorrhages in Werlhof's disease. We feel that such a conclusion cannot reasonably be drawn from one case and that this report can be interpreted only in the light of future findings. These authors reported also an increase in the amount of albumin in the serum with this treatment and expressed the opinion that this may be a factor in stopping the bleeding. The increase they reported was from 5.02 mg. to 6.39 mg. per hundred cubic centimeters. They studied these changes further and reported<sup>36</sup> that both in persons with hemorrhagic conditions and in normal subjects the administration of 100 mg. of cevitamic acid daily resulted in a marked increase of the total amount of protein. This was first noticeable after the third day, the increase was largely confined to the albumin fraction while the values for globulin and fibrinogen were little changed.

In a recent communication<sup>37</sup> Professor Szent-Gyorgyi reported favorable results in cases of hemorrhagic nephritis, purpura, pyuria, pyorrihea and aggranulocytosis. The dosage used was from 150 to 200 mg. on alternate days.

Before proceeding with a summary of our experience with the use of this drug, we feel that a brief discussion of a test which we have found most useful in evaluating the clinical course of these diseases is in order. For the past five years we have been especially interested in a study of human capillaries<sup>38</sup> and throughout this time have been seeking a satisfactory and simple test of capillary fragility. None thus far has been entirely satisfactory,<sup>39</sup> but we have found the following modifi-

36. Boger, A., and Schroeder, H. *Klin. Wchnschr.* **23**: 842, 1934.

37. Szent-Gyorgyi, A. Personal communication to the authors Nov. 27, 1934.

38. Durjee, A. W., and Wright, I. S. *Am. J. M. Sc.* **185**: 664 (May) 1933. Wright, I. S. The Clinical Value of Human Capillary Studies, *J. A. M. A.* **101**: 439 (Aug. 5) 1933. Wright, I. S., and Durjee, A. W. Human Capillaries in Health and in Disease, *Arch. Int. Med.* **52**: 545 (Oct.) 1933. Wright, I. S., and Moffat, D. The Effects of Tobacco on the Peripheral System, *J. A. M. A.* **103**: 318 (Aug. 4) 1934.

39. Cutter, Irving and Marquardt, Gilbert. *Proc. Soc. Exper. Biol. & Med.* **28**: 113 (Nov.) 1930. Hess, A. F. Recent Advances in Knowledge of Scurvy and the Antiscorbutic Vitamin, *J. A. M. A.* **98**: 1429 (April 23) 1932. Dalldorf, G. A Sensitive Test for Subclinical Scurvy in Man, *Am. J. Dis. Child.* **46**: 794 (Oct.) 1933. Lindberg, A. *Hygiea* **95**: 10 (Jan. 15) 1933. Gothlin, G. F. *J. Lab. & Clin. Med.* **18**: 484 (Feb.) 1933. Stocking, R. E. *Arch. Pediat.* **50**: 823, 1933. Greene, D. Evaluation of the Capillary Resistance Test in the Diagnosis of Subclinical Scurvy, *J. A. M. A.* **103**: 4 (July 7) 1934.

cation of the tourniquet test (Rumpel-Leede phenomenon) to be sufficiently standardized to be of great value

A circle 2.5 cm in diameter, the upper edge of which is 4 cm below the crease of the elbow, is drawn on the inner aspect of the forearm. Any skin blemishes within the circle which could possibly be confused with petechiae are marked with ink. The rubber cuff of a mercury blood pressure manometer is then applied as usual around the upper part of the arm and inflated to a pressure midway between the systolic and the diastolic pressure of the patient. This is maintained for fifteen minutes, after which the pressure is released, at the end of five minutes the number of petechiae within the circle is counted with the naked eye. From many observations we believe that an absolutely normal count is rarely above 10, that there is a marginal zone between 10 and 20 and that a count above 20 is definitely abnormal. We have attempted to standardize this test so that all workers might be able to discuss their results with mutual understanding and have tried at the same time to keep it free from a need for special apparatus, so that it might have universal use. We found the zone of the crease of the elbow to be tremendously variable in the numbers of petechiae produced, without corresponding significance. There does appear to be a downward gradient below the elbow, and 4 cm was taken as an arbitrary distance, far enough from the irregularities of the crease of the elbow. Two and five-tenths centimeters for the diameter is also arbitrary, being sufficient to encompass a fair-sized area but not too large to permit of ease in counting the petechiae. As a further refinement, two or three circles of this size might be drawn at the same level and the average count of the two or three taken. The cuff pressure suggested might well be criticized, but we aimed merely to arrive at a pressure which guaranteed a greatly increased capillary pressure with no venous escape. We deprecate the use of a magnifying glass to count the petechiae as merely complicating the situation and not adding practically to the information.

In certain patients, because of discomfort or excessive subcutaneous hemorrhages, it may be desirable to use seven and a half minutes instead of fifteen minutes as the standard. All further readings taken on the same person should be taken with the modified time. This test may be done every four days or alternate arms (thus giving the capillaries of each arm from seven to eight days to heal).

We readily admit that other conditions in addition to scurvy may produce or increase the number of petechiae and also that other factors, such as season, race and edema and, rarely, the menses, may cause fluctuations. This test is, nevertheless, as we shall demonstrate later in this paper, a valuable aid, not only in the study of these conditions but also as a guide to therapeutic results.

Another problem which needs clarification at this point is the incidence of vitamin C deficiency in adults. It has become increasingly evident that in spite of the publicity given vitamins and the available supply of citrus fruits there are many cases of C avitaminosis, the milder of which are usually unrecognized. In the course of nine months we have seen twenty patients for whom a diagnosis of vitamin C deficiency could be reasonably established. The chief causes have been dietary—diets conditioned by poverty and diets prescribed by the medical pro-

fession or chosen by the patient, either because of preference or because of adherence to some food faddism. We have seen even severe evidences of scurvy which have developed as a result of diets prescribed for ulcer, colitis and urticaria and which have been unrecognized by the attending physician. It must be acknowledged that many of these cases represent a mixed avitaminosis and also that there are many more which are "subclinical." This subject was well reviewed by Mettier, Minot and Townsend in 1930.<sup>40</sup>

Another much rarer group of patients appears to be unable to utilize a vitamin intake which should be fully adequate. Although in principle this possibility was suggested by Fenwick<sup>41</sup> and others, Castle and Locke<sup>42</sup> were the first to demonstrate clearly that irrespective of the adequacy of the diet certain abnormalities in the gastric secretion might condition a state of dietary deficiency. Strauss<sup>43</sup> discussed this problem in relation to certain deficiencies in 1934. Jackson<sup>44</sup> demonstrated that vitamin A, if it was ingested at approximately the same time as liquid petrolatum, could be carried through the intestinal tract without absorption. That vitamin C may be unused, though taken in adequate amounts, is suggested by several interesting observations, the first is that a scorbutic-like syndrome may develop while a person is taking large amounts of citrus fruit (from two to three oranges a day), and the second, that certain workers<sup>27</sup> noted that some scorbutic patients failed to respond to fruit juice or cevitamic acid given by mouth but responded and recovered when given cevitamic acid intravenously. We have confirmed this finding and have induced a relapse by placing several such patients on a regimen of vitamin C by mouth, they have been recured with cevitamic acid administered intravenously. The mechanism producing such a phenomenon certainly is not understood, but the following possibilities suggest themselves: (a) anacidity or imbalance of the gastric secretion, (b) bacterial destruction of the vitamin in the upper part of the gastro-intestinal tract, (c) inflammatory changes of the intestinal mucous membrane, (d) accelerated action of the intestinal tract due to diarrhea of a variety of causes, including laxatives, (e) the use of oily laxatives which may hold the vitamin, as already demonstrated with vitamin A, and finally (f) changes which may take place after absorption but which render the vitamin inert.

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40 Mettier, S. R., Minot, G. R., and Townsend, W. C. Scurvy in Adults Especially Effect of Food Rich in Vitamin C on Blood Formation, *J. A. M. A.* **95** 1089 (Oct 11) 1930.

41 Fenwick, Samuel. On Atrophy of the Stomach and on the Nervous Affections of the Digestive Organs, London, J. & A. Churchill, 1880.

42 Castle, W. B., and Locke, E. A. *J. Clin. Investigation* **6** 2 (Aug.) 1928.

43 Strauss, M. B. The Role of the Gastro-Intestinal Tract in Conditioning Deficiency Disease, *J. A. M. A.* **103** 1 (July 7) 1934.

44 Jackson, R. W. *J. Nutrition* **4** 171 (July) 1931, *ibid* **7** 607 (June) 1934.

As criteria of "subclinical" or early scurvy, we used the history of a diet poor in vitamin C taken over a protracted period of time, a definite increase in capillary fragility on several checked tests and a response by a decrease in capillary fragility to within the normal range (0-10) on exactly the same regimen with the single addition of cevitamic acid <sup>45</sup>

#### VITAMIN C DEFICIENCY

The first series of cases which we report is grouped under the heading of vitamin C deficiency. Three of these cases have been briefly reported elsewhere <sup>46</sup>

Chart 1 shows graphically the effect of vitamin C (cevitamic acid), whether taken by mouth or intravenously, on the capillary fragility. Without exception it was possible to reduce the number of petechiae to less than 15, and in only one patient (F K), whom we could not follow longer, was the final figure above 10, the figure we consider to represent the upper limit of normal. Patient R B is of especial interest, since her capillary fragility improved from 63 to 14, then, when she once more was on a diet very low in vitamin C, because of poverty, the capillary fragility remounted to 70. Once more it was possible by using 0.09 Gm daily by mouth to reduce the number of petechiae from 70 to 10 in two weeks. Patients E and N also received other concentrated vitamins to supplement treatment, so their curves may be considered of less value. We have not noted, however, that other vitamins influence capillary fragility.

Each case history will be discussed separately.

CASE 1—W J, a male nurse, aged 52, was first seen on May 20, 1934. He had had a distaste for fruits all his life and had been on a diet deficient in vitamin C for many years. According to his own statement, he did not believe that he "took one piece of fruit a year." For the previous three months, because of a condition diagnosed as "colitis and possible malignancy," he had been on a diet consisting of cream, eggs, rice and soda crackers with an occasional piece of breast of chicken. He had been taking tincture of belladonna, 15 drops three times a day. He smoked from eight to ten pipefuls of tobacco a day. At this time his complaints were loss of weight, nasal hemorrhages, bleeding gums, bleeding from the rectum, marked discomfort with a sense of a mass in the rectum and extreme weakness, which made it difficult for him to walk even a very short distance.

Physical examination revealed the following. The gums were soft and bleeding and the teeth very loose. There were perifollicular cutaneous hemorrhages on both legs about the knee and on the left shoulder anteriorly, there were multiple subcutaneous hemorrhagic areas, averaging 2.5 cm in diameter, over the tibias.

The capillary fragility test showed 90 petechiae. The blood pressure was 110 systolic and 70 diastolic. The blood count revealed white cells, 7,400, red cells,

<sup>45</sup> All cevitamic acid used in this study was supplied by Merck Co., Inc.

<sup>46</sup> Wright, I. S. *Proc Soc Exper Biol & Med* **32** 475 (Dec) 1934.



4,600,000, hemoglobin, 106 per cent (Sahli), and platelets, 190,000. The bleeding time was four minutes, and the clotting time, four minutes. The differential count revealed polymorphonuclears, 69 per cent, small lymphocytes, 13 per cent, large lymphocytes, 15 per cent, eosinophils, 1 per cent, and basophils, 2 per cent.

May 23 The patient weighed 112 pounds (50.81 Kg). He was instructed to maintain exactly the same diet previously described (a diet low in vitamin C) and was given crystalline vitamin C, 0.02 Gm orally, three times a day.

June 1 According to the patient, the gums were no longer bleeding, the teeth were firmer, there were no new perifollicular or subcutaneous hemorrhages and there had been a diminution of nasal and rectal bleeding. The capillary fragility test showed 90 petechiae (no change). The patient was instructed to continue the crystalline vitamin C, 0.06 Gm a day orally.

June 7 The patient reported a great general improvement and a marked increase in strength. He said that he had had no further nasal hemorrhages or

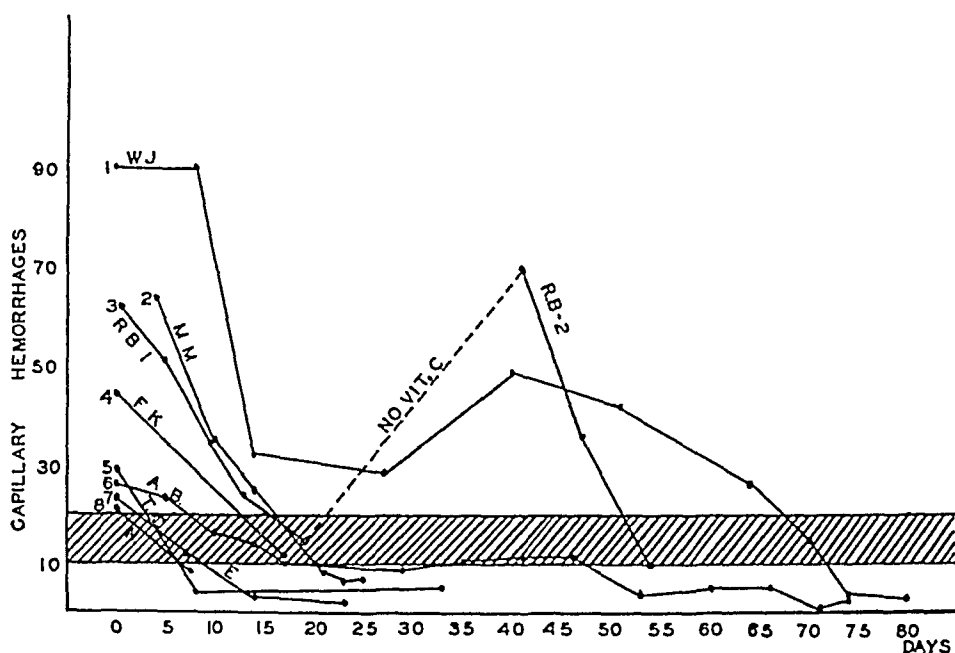


Chart 1—The effect of cevitamic acid on the capillary fragility in eight cases of vitamin C deficiency

purpuric spots and had had on an average only one bloody stool each day instead of continuous bloody diarrhea. The capillary fragility test showed 32 petechiae.

June 19 The improvement continued. The gums appeared more normal. The teeth were firmer. The capillary fragility test showed 29 petechiae. The weight had increased to 129½ pounds (58.7 Kg), and there was a great increase in strength.

July 3 The improvement continued. Rectal bleeding was rarely noticed. The gums were normal and did not bleed. The teeth were firm in the sockets. The weight was 132½ pounds (60.1 Kg). The capillary fragility test showed an increase to 49 petechiae. Up to this point the patient had continued taking 0.06 Gm of cevitamic acid a day. At this time he was instructed to take 0.1 Gm daily, in view of the increase in the number of petechiae.

July 13 He continued to feel stronger, with very rare rectal bleeding. The teeth were absolutely solid and the patient reported that he believed that he would

be able to chew tough foods, if permitted. He weighed 134 pounds (60.8 Kg). The capillary fragility test showed 42 petechiae. He was then instructed to take 0.09 Gm of cevitamic acid orally each day and to continue on the diet low in vitamin C.

July 27 Continued improvement was reported. Rare small spots of blood were noted in the stool. No bleeding was seen elsewhere. The weight was 135½ pounds (61.4 Kg). The capillary fragility test showed 26 petechiae.

August 4 The patient reported that he considered himself in perfect health and that he "couldn't feel better." Rare, slight streaks of blood or mucus were seen in the stool. The weight was 139 pounds (63 Kg). The capillary fragility test showed 15 petechiae. The patient had been at work for the previous week, which necessitated his walking from 8 to 10 miles a day, and he felt perfectly capable of performing this exercise without undue fatigue. The dosage of cevitamic acid was reduced to 0.06 Gm orally each day.

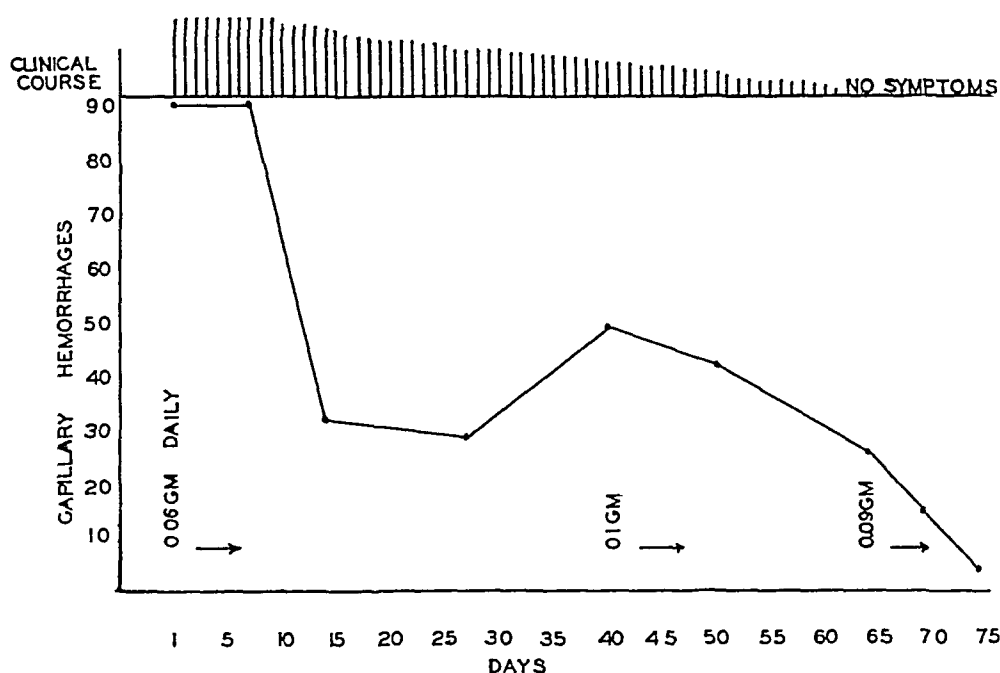


Chart 2—The effect of cevitamic acid administered orally on the capillary fragility of patient W J

August 15 The patient's complaints and the results of the physical examination were negative as far as any evidence of the scorbutic condition could be determined. He reported no mucus with his stools. The weight was 142 pounds (64.4 Kg). The capillary fragility test showed 4 petechiae. The patient was then placed on a general diet high in vitamins and was discharged.

NOTE—Throughout the study of this case the capillary fragility tests were done with the Baumanometer blood pressure machine at the half-way mark between the diastolic and the systolic pressure for fifteen minutes.

Comment—The clinical course in this case is interesting and significant. Moderate scurvy developed as a result of the patient's native dislike for fruits containing vitamin C. As we review the clinical course under treatment, it seems probable that the hemorrhages from the bowels were severe manifestations of the scorbutic syndrome. The

medical attendant, failing to recognize this, treated the patient for a hemorrhagic form of colitis and placed him on a bland diet poor in vitamin C. On this regimen, the scorbutic syndrome, associated with a marked loss of weight and increased weakness, continued to develop. The fact that merely by adding crystalline vitamin C to the diet which had accentuated the pathologic condition we were able to produce a complete reversal of symptoms, with a steadily progressive improvement in each aspect, was particularly interesting. This improvement included complete cessation of hemorrhage and its accompanying discomfort, decrease in capillary fragility to well within normal limits, a gain in weight from 112 to 142 pounds (50.8 to 64.4 Kg.), and such a gain in strength that instead of being barely able to walk he was enabled to carry on a daily occupation which necessitated from 8 to 10 miles of walking.

CASE 2—M. M., aged 57, a Polish Jew, had lived for years on a depleted diet, which for more than one year before his admission to the Bellevue Hospital (April 12, 1934) had contained practically no foods which could be considered sources of vitamin C (fresh fruits, fresh green vegetables, liver, etc). One year before he had been confined to another hospital with pains in his legs. For three weeks before admission he had felt "sick all over," with generalized aching. He had had no food for four days preceding admission. On physical examination he presented the classic picture of adult scurvy, with the following positive findings: poor nutrition, disorientation, bleeding with very marked erosion of the gums, large subcutaneous hemorrhages in the areas of the left thigh, left knee and both legs (these areas varied in size up to about 6 square cm.), multiple small perifollicular hemorrhages scattered over the extremities and extreme tenderness over both legs and over the humerus, radius and ulna of both arms. In addition, he showed moderate cardiac enlargement, generalized arteriosclerosis, early clubbing of his fingers (unexplained) and a large scrotal hernia on the right side.

April 13. On the basis of the diagnosis of scurvy, the patient was placed on a diet high in caloric and vitamin content, with the forcing of citrus fruit juices, of which he received from 180 to 300 cc. a day. A moderate secondary anemia was present, which improved with vitamin C therapy.

The Wassermann and van den Bergh tests and urinalysis gave negative results. Throughout the patient's stay in the hospital his pulse, temperature and respiratory rate showed no significant variations. His blood pressure was 170 systolic and 100 diastolic and later 140 systolic and 84 diastolic. Roentgenograms of the extremities did not show definite subperiosteal hemorrhages.

April 17. After four days on the diet high in vitamins, the general condition was much improved. There were no new hemorrhagic areas, and the gums bled less readily. The patient was slightly more alert mentally.

April 24. On the eleventh day of treatment his progress had been steady but slow. No new hemorrhages had occurred, the gums were less tender, but mentally the patient was semirational, with periods of lucidity. His blood pressure was 130 systolic and 80 diastolic. The capillary fragility test made at this time, after eleven days of a diet high in vitamin C, showed 39 petechiae. The patient was then placed on a diet free from vitamin C, consisting of cereals and bread-stuffs.

April 28 After four days on this restricted diet he was definitely worse His gums bled spontaneously, and he was practically comatose, with periods of irrationality The capillary fragility test produced 64 petechiae, corresponding to the definite progression of the scorbutic syndrome He was then kept on the scurvy-producing diet, with the addition of cevitamic acid, 0.02 Gm orally three times a day

May 4 In seven days he showed a remarkable general improvement His mental condition was markedly cleared He held a rational conversation and expressed a desire to sit up His gums still bled on pressure, but he had had no new hemorrhages, and all tenderness had disappeared The capillary test showed 35 petechiae

May 8 On the twelfth day of the cevitamic acid regimen the patient was absolutely clear mentally (although his intelligence quotient was low) He held

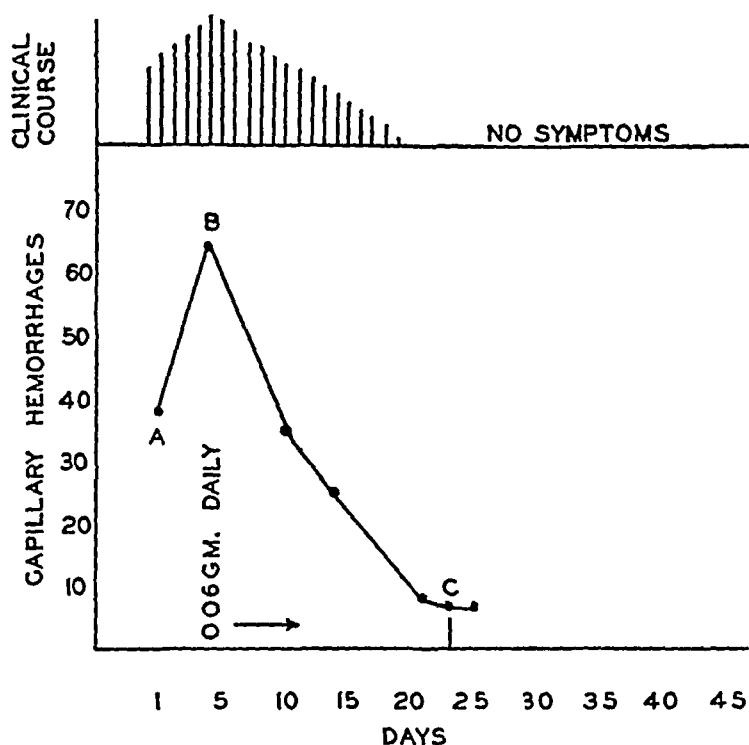


Chart 3—The effect of cevitamic acid administered orally on the capillary fragility of patient M M

long conversations in English and Polish He was allowed to sit up and desired to go home His gums appeared secondarily infected, and examination revealed organisms resembling Vincent's The capillary fragility test produced 25 petechiae

May 14 On the eighteenth day the capillary fragility test produced 8 petechiae, which is considered to be within the normal limits The patient had been out of bed each day

May 16 On the twentieth day a recheck showed 7 petechiae The patient was then placed on a regular, well balanced diet with a high vitamin C content

*Comment*—This case is of especial interest in that the scorbutic syndrome was definitely improved with the ingestion of citrus fruits, made worse by a diet poor in vitamin C and cured by the addition of only cevitamic acid to the diet which was responsible for the relapse

The results of the capillary fragility test followed the clinical course very closely

CASE 3—R B, a woman aged 52, was seen with the complaint of weakness and pain and swelling of both ankles, especially the right, of three weeks' duration. Bilateral salpingectomy had been performed twenty years before. One and a half years before glaucoma developed over the eyes. Because of poverty, she had been on a markedly depleted diet for the year immediately preceding this examination. During this time she had taken very little food containing vitamin C and during the last month had had no appreciable amounts of vitamin C.

Physical examination showed a fairly well developed but chronically ill woman. Her few remaining teeth were carious. Her gums were spongy, oozed blood slightly and bled easily on pressure. The abdomen was normal except for a suprapubic scar from an old salpingectomy. Abdominal reflexes were not elicited. There was edema of both ankles, especially the right. The knee jerks were not elicited. The blood pressure was 180 systolic and 120 diastolic.

The Wassermann reaction was negative. The urine was normal, and the platelets numbered 190,000. The capillary fragility test showed 61 petechiae in fifteen minutes.

The patient was given 0.09 Gm of cevitamic acid orally a day. Her general condition improved markedly. The edema cleared up. The capillary fragility was markedly decreased, as noted on chart 1. On the twenty-sixth day there were only 14 petechiae seen after a fifteen minute test.

The patient then left the hospital and once more was on a very depleted diet, with an inadequate supply of vitamins, because of poverty. Twenty-two days later she returned to the hospital after having had a recurrence of her weakness and edema. The capillary fragility test once more showed an increase to 70 petechiae in fifteen minutes. Although we were unable to improve the patient's general diet appreciably, she was given a supply of cevitamic acid which enabled her to take 0.12 Gm orally a day. After seven days the capillary fragility test showed 36 petechiae, and after another seven days, 10 petechiae. The edema had cleared up completely.

*Comment*—This case seems to be a true instance of malnutrition in which lack of vitamin C was one of the major factors. It is recognized that in all cases of malnutrition there is probably a mixed avitaminosis, but this patient responded very quickly and satisfactorily to the addition of large amounts of vitamin C alone. The fact that when the patient abstained from vitamin C she had a recurrence of her condition and that it once more cleared up when the vitamin was used would seem to establish beyond question the value of cevitamic acid in her case.

CASE 4—F K, a woman aged 48, was first seen on June 27, 1934. Her chief complaint was innumerable subcutaneous hemorrhages with marked epistaxis at night and hematuria. Careful inquiry into her dietary history revealed that for many years she had had an aversion to citrus fruits and other sources of vitamin C.

Physical examination gave essentially negative results, except for a questionable mass and slight tenderness over the left flank and costovertebral region. Complete studies of the blood, including red cell count, white cell count, differential count and determinations of hemoglobin, bleeding and clotting time, cell fragility

and coagulation time, were made and checked several times, the results being within normal limits. The capillary fragility test, however, revealed 43 petechiae after ten minutes, the patient being unable to continue the test longer because of discomfort.

The patient was placed on a regimen of 0.06 Gm. of cevitamic acid by mouth daily for two weeks and then 0.09 Gm. daily for three days. At the end of that period the capillary fragility test revealed 11 petechiae in ten minutes. During this time studies of the urinary tract indicated a renal tuberculosis on the left side, and on July 12 nephrectomy was performed. Before the operation the nasal hemorrhages had ceased and only an occasional purpuric spot was noted. The patient was discharged thirteen days later, on July 25. No cevitamic acid was given from July 12 to July 20, following immediate operative convalescence. After that period she was given 0.06 Gm. orally per day. No purpuric spots or hemorrhages were noted after the operation.

The patient did not return for further follow-up study.

*Comment*—The question may well be raised as to whether this case should be classified as one of early vitamin C deficiency produced by lack of intake over a prolonged period of time, whether the patient represents one of those persons who, in addition, because of the presence of an infection, appear to drain their vitamin C resources more rapidly or whether the case be classified as one of nonthrombocytopenic purpura associated with a low grade chronic infection. In favor of the scorbutic diagnosis is the fact that both the clinical course and the capillary fragility improved considerably before operation with the administration of cevitamic acid.

CASE 5—T. C., a woman aged 22, was first seen on July 13, 1934. Her chief complaint was severe pain in the midepigastrium, especially from two to three hours after eating. It was formerly relieved by alkalis and food but not relieved by any medication during two weeks preceding examination. Four days before admission the patient had a severe gastric hemorrhage. Four years previous to this time she had symptoms resembling those of a peptic ulcer. Following inadequate study a surgeon did a partial gastrectomy, but the pathologic examination of the tissue revealed only acute gastritis. Ever since then the patient had been on a diet practically free from fruit and fresh uncooked vegetables. For the first six months following the operation she had had no symptoms, but since that time she had had the symptoms typical of a duodenal ulcer. Six months before admission she had her first gastric hemorrhage.

After being placed on a Sippy diet, her symptoms diminished but did not disappear, and, as noted previously, she had another severe hemorrhage just previous to admission. The capillary fragility test on admission showed 27 petechiae. She was placed on a Sippy diet with alkalis and was given 0.06 Gm. of cevitamic acid daily by mouth. On the fifth day the capillary fragility test showed 4 petechiae, and twenty-five days later the count had not risen above the level of 6 petechiae.

*Comment*—It is not our purpose to discuss in detail the diagnosis and treatment of the marginal ulcer which was revealed in the roentgenogram of this patient. From the point of view of the problem we are discussing, however, several points are very important. One is the

evident need for the inclusion of an adequate source of vitamin C in the diets of patients who are on modified diets for ulcer over a long period of time. The very stringency of these diets, particularly in reference to foods containing vitamin C, would tend to increase the likelihood of increased capillary fragility and hence may predispose to free bleeding from the ulcers. The second point of interest is that this patient was able to take cevitic acid within a few days after having had a hemorrhage without any signs of gastric irritation. In fact, she stated that on repeated tests the cevitic acid appeared to relieve her discomfort more satisfactorily than the alkali powders prescribed. The third point of interest is a definite improvement in capillary fragility, as evidenced by the use of capillary fragility tests.

CASE 6—A B, a woman aged 57, was first seen on Sept 10, 1934. The chief complaints at the time of admission were extreme general weakness, vomiting, pain and weakness of the right side of the face and multiple large purpuric spots (from 2 to 5 cm in diameter) scattered over the left arm, the left hip and both legs, of one week's duration.

Appendectomy was performed twenty-seven years previously. Intermittent pain in the epigastrium was diagnosed twelve years previously on roentgen examination as a duodenal stricture. The patient had never vomited blood, nor had she had tarry stools. Cholecystectomy was performed twelve years previously. Thyroidectomy was performed eight years previously, at which time the parathyroid glands were partially removed because of enlargement, the exact pathologic process of this enlargement has not been definitely established. Four years previously the patient fell, fracturing one vertebra. Five months previously she fell, fracturing both humeri. During the six years previous to this time she had scattered over the trunk and extremities a constant succession of large purpuric spots, each of which had taken from five to six weeks to disappear. She had always taken large amounts of citrus fruits and fruit juices. The weight was 135 pounds (61.2 Kg).

On physical examination the patient appeared chronically ill, with moderate pallor. There was palsy of the right side of the face, with a distribution typical of Bell's palsy. There was a thyroidectomy scar. A rough systolic murmur was heard over the apex of the heart, transmitted toward the base. The abdomen was normal except for scars following an upper right rectus and a McBurney incision. The cervix was slightly eroded and bilaterally lacerated.

Rectal examination revealed internal hemorrhoids but no bleeding. Examination of the skin showed large purpuric spots, ranging from 2 to 5 cm in diameter, scattered over the left arm, the left hip and both legs. The blood pressure was 162 systolic and 78 diastolic. Laboratory studies showed the following: blood cultures, negative; basal metabolism, plus 117 per cent; electrocardiographic tracing, negative. The results of gastric analysis follow:

	Hydrochloric Acid		
	Free	Combined	Total
Fasting content	0	19	19
½ hour (after 75 cc of 7 per cent alcohol)	16	33	49
1 hour	23	13	36
Lactic acid—0			
Occult blood—0			

The blood count revealed red blood cells, 4,230,000, hemoglobin, 86 per cent, white blood cells, 5,700, polymorphonuclears, 68 per cent, band forms, 7 per cent, leukocytes, 22 per cent, and mononuclears, 22 per cent. The Wassermann reaction of the blood was negative. The red cells showed slight variation in size and shape. There was moderate polychromatophilia.

On September 10 the platelet count was 90,000. The capillary fragility test showed 26 petechiae in seven and one-half minutes. The bleeding time was from one and one-half to two minutes, the coagulation time, from four and one-half to five minutes.

The patient was given cevitic acid intravenously. The first dose was 0.05 Gm, and thereafter she was given a daily injection of 0.1 Gm. Beginning with the fourth day the patient reported feeling much stronger and generally better. The purpuric spots had almost entirely cleared up, and no new ones were noted.

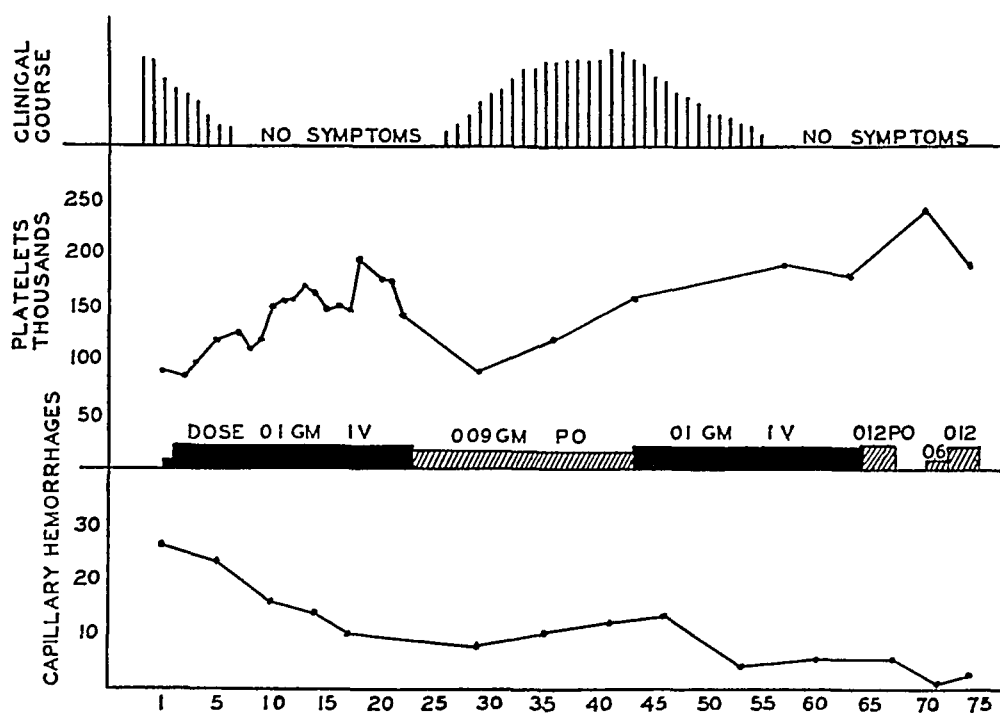


Chart 4—The effect of cevitic acid on patient A B

Seven days after the first injection the patient was discharged from the hospital. She claimed at this time that she felt well enough to return to her work. She continued to receive daily injections of cevitic acid intravenously. Chart 4 shows the changes in the platelet count and capillary fragility which took place over a period of seventy-five days of observation.

After the twentieth injection, in order to simplify treatment, the patient was given cevitic acid orally, 0.09 Gm daily. At that time, she was feeling very well and had had no new purpuric spots, but shortly after she began to feel less strong, and new purpuric spots appeared. This became more pronounced, until on the sixteenth day of oral administration was begun she fainted and was readmitted to the hospital. Her condition was essentially the same as it had been on the previous admission, except that the palsy on the right side of the face had entirely cleared up. Three or four purpuric spots, from 1 to 2 cm in diameter, were seen above the right ankle and the right eyelid.



On the sixth day after admission she was again placed on a regimen of intravenous medication with cevitamic acid, 0.1 Gm per day. During this admission roentgenograms of the gastro-intestinal tract showed no organic pathologic process. The basal metabolism was plus 10.9 per cent. The red blood cells numbered 4,200,000, and the hemoglobin content was 76 per cent. The white blood cells numbered 6,600, with a normal differential count. The urine was normal. The calcium content of the blood was 10 mg per hundred cubic centimeters, the phosphorus content, 4.1 mg. The blood pressure was 160 systolic and 70 diastolic.

The patient showed marked improvement in strength, there was no recurrence of purpuric spots on the intravenous administration of cevitamic acid. She was discharged from the hospital after seventeen daily injections.

She continued to receive 0.1 Gm per day intravenously and felt very much stronger for ten days. At the end of this period she was given 0.12 Gm orally per day (4 tablets, 0.03 Gm per tablet, three times a day). After fourteen days on this regimen she reported that she had continued to improve, that she had had no purpuric spots, that she had gained in weight from 135 to 152 pounds (61.2 to 68.9 Kg), that her appetite had returned and that she no longer suffered from insomnia, which had been a chronic complaint for a long time. (Since the completion of this study the patient has had three episodes, each characterized by collapse and the appearance of purpuric spots, subsequent to the use of cevitamic acid by mouth. Intravenously administered cevitamic acid has produced marked improvement following each of these attacks.)

*Comment*—This case presents a syndrome which is difficult to classify. The platelet count was definitely lowered, and there was evidence of subcutaneous bleeding. These facts might lead one to believe that the patient was suffering from mild thrombocytopenic purpura. The history of taking large amounts of citrus fruits would tend to influence the diagnosis away from scurvy, and yet we have seen a number of patients who apparently cannot utilize vitamins, even when they are adequately taken. This has been stressed recently by several authors. The fact that this patient responded so well to intravenous medication and rather poorly to cevitamic acid by mouth during the first attempt would lead one to believe that she might fall within that group. This has been further confirmed by the fact that she has had three subsequent episodes characterized by the onset of purpuric spots and great weakness. Each of these attacks has cleared up with the use of cevitamic acid intravenously. The patient is at present recuperating slowly from the shock of a Colles fracture. It should be noted in the report on the gastric analysis that free hydrochloric acid was absent until the alcohol was given. This has been reported as frequently associated with the group of persons who cannot utilize vitamin C taken by mouth.

We shall not attempt an explanation of the increased platelet count associated with the administration of cevitamic acid. It is noteworthy that it reached high levels on several occasions (191,000 and 240,000) but failed to remain there, although the administration of cevitamic acid was continued. On the other hand it is clear that the average daily

level was much higher from the ninth injection throughout the remaining sixty-six days. The result of the capillary fragility test was not markedly high at the beginning (26 petechiae in seven minutes), although if the patient could have tolerated the discomfort of the Baumanometer cuff for fifteen minutes it would have been higher. The number of petechiae has decreased with successive readings and has been well within normal during the past month.

CASE 7—E, a widow aged 63, a German, until eight or nine years before this examination had been free from any illness of importance which might have had a bearing on the present problem. She became disturbed about an unhappy marriage of one of her daughters, lost her appetite and then started to drink immoderately, thus forming a habit which further decreased her food intake.

About ten years previously she had remarried, marrying a man who demanded a great deal of domestic attention, i. e., as to clothing, meals, etc., and who ate only heavy, hearty food, such as corned beef and cabbage, sauerkraut, potatoes, etc. This resulted in her eating small amounts of vegetables, fruit, milk, etc. Six years ago she began to feel weak, and five years ago she had a massive rectal hemorrhage. Her physician diagnosed her condition as ulceration of the bowel, placed her on a diet of milk, cream and soda crackers, and prescribed  $\frac{1}{2}$  gram (0.032 Gm.) of morphine to be taken at any time for pain and hemorrhage. This continued until the spring of 1934, when her physician died, and his nephew, who assumed his practice, ordered her to discontinue the morphine and replace it with alcohol. She continued to take camphorated tincture of opium, which she obtained from drug stores, but, in addition, began to drink enough alcohol to result in frequent intoxication. Her abdominal pain became worse, with colicky paroxysms. Her stools were mucopurulent and bloody. She could not eat regular food or take fruit juices because of gastro-intestinal distress. A sore tongue, bleeding, swollen, painful gums and loose teeth developed. She bruised very easily. The backs of her hands became hardened and rough.

The significant physical findings were as follows: obesity, disorientation, constricted pupils (morphine), foul breath, loose teeth, swollen, bleeding, dirty gums, a red, swollen, smooth tongue, large purpuric spots about the left shoulder joint, the left thigh and scattered elsewhere over the body and rough, thickened, brownish, discolored skin on the dorsa of the hands. The data from laboratory tests is shown in the table.

#### *Results of Laboratory Tests*

Date	Capillary Fragility Test	Platelets	Red Blood Cells	Color Index
9/19/34	19			
9/24/34	Patient put on 0.06 Gm. of cevitamic acid orally daily			
9/24/34	23	60,000	3,750,000	0.8
10/1/34	12	140,000	4,230,000	0.8
10/8/34	4	175,000	4,720,000	0.85
11/17/34	2	220,000	4,610,000	0.9

Unfortunately, from the point of view of controlled observation, this patient received large amounts of other vitamins and fruit juices also during treatment. The consumption of alcohol was stopped. The patient was unable to take regular foods and especially fruit juices at first, because of resultant discomfort, but during this time she did take cevitamic acid. It seemed to relieve the pain (so

she claimed), and she believed that it was given for that purpose (Note case 5 in which similar results are reported) After seven weeks on this regimen the patient appeared to be in perfect health, walking and talking spiritedly, with no symptoms referable to the gastro-intestinal tract and with an excellent appetite

*Comment*—This case probably represents another example in which scurvy was diagnosed as ulcerative colitis and made much worse by the dietary regimen ordered by the physician The capillary fragility test and platelet count showed curves which followed closely the clinical improvement, and they became normal when cure was effected

It cannot be claimed that cevitamic acid is solely responsible for the cure in this instance, but it was important that it could be given by mouth before the patient could tolerate fruit juices It may be of no significance, but it should be noted that the patient in case 5 and this patient both spontaneously stated that the cevitamic acid seemed definitely to relieve the pain in the gastro-intestinal region

CASE 8—N, a trained nurse, aged 45, for two years had been on a severely restricted diet on account of a cutaneous condition Review of this diet at once raised doubt as to its sufficiency Physical examination suggested a mild scorbutic state because of the condition of the gums and the presence of black and blue spots The capillary fragility test showed 21 petechiae in fifteen minutes One week of 0.06 Gm of cevitamic acid daily by mouth and a diet high in vitamins brought the count down to 9 The patient felt so much better that she stopped coming because of distance and cost of travel

*Comment*—The report of this case is included to record another instance of the production of mild scurvy as a result of a therapeutic diet, the tolerance to cevitamic acid and the marked improvement in the capillary fragility and the clinical picture following its use with other vitamins

It should be noted that we have not found that the use of other vitamins without vitamin C will affect the capillary fragility

Twelve additional patients with marked scurvy have been promptly cured by the addition of crystalline vitamin C to their previous scurvy-producing diets This brings this series to a total of twenty

#### PURPURA

The next group of patients to be considered consists of those whose condition is included under the heading of "Purpura" This series is admittedly too small for general conclusions to be drawn from it, but the individual case studies are instructive As may be noted from a study of the histories, although large doses of cevitamic acid were given intravenously, we had no evidence of a favorable effect on the clinical course, the capillary fragility or the laboratory studies in any of these patients We might, however, if we had not continued our observations

of patient M G over a protracted period of time under careful control, have drawn an erroneous conclusion in this regard

CASE 1—M G, a woman aged 45, had had bleeding gums and nasal bleeding for two years. Many purpuric spots and showers of petechiae had been present for three years. This tendency to bleed had been much more marked during the two months preceding examination, with the patient bleeding very freely from the gums, the nose and during menstrual periods. The dietary history revealed that she had been on a diet very low in vitamin C because of poverty and had had only an occasional piece (one in two to three months) of citrus fruit.

Physical examination revealed frank bleeding from the nose and gums, a large number of purpuric spots scattered over the entire body and bleeding from the cervix.

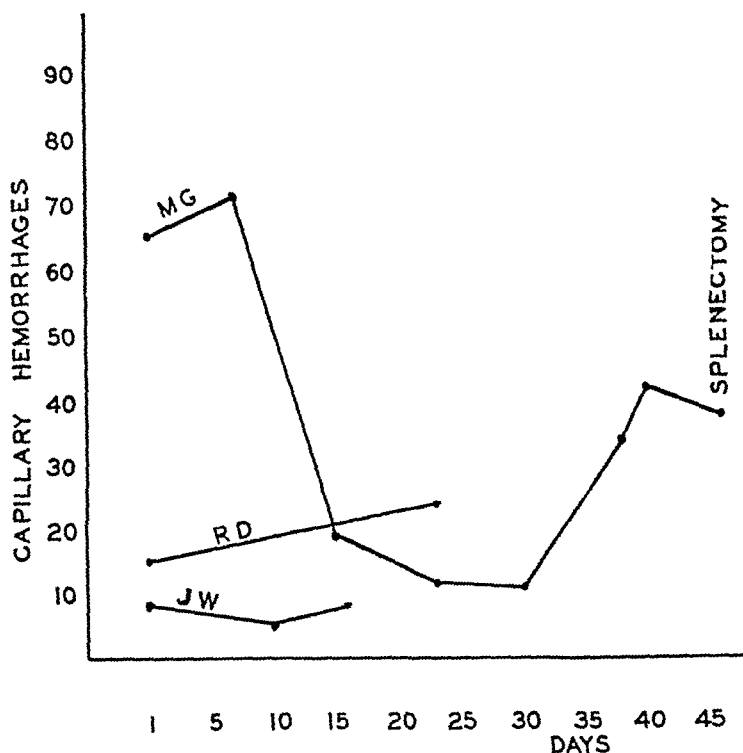


Chart 5—The effect of cevitic acid on the capillary fragility in three cases of thrombocytopenic purpura

Oct 24, 1934 The capillary fragility test showed 65 petechiae after seven and a half minutes. The platelet count was 60,000. The patient was placed on cevitic acid, 0.09 Gm daily by mouth. The capillary fragility tests, platelet counts and clinical course are graphically represented in chart 6.

October 30 Other laboratory studies gave the following results: red blood cells, 3,480,000, hemoglobin, 36 per cent, reticulocytes, 3.8 per cent, white blood cells, 8,500, polymorphonuclears, 50 per cent (band forms, 5 per cent), lymphocytes, 40 per cent, mononuclears, 3 per cent, eosinophils, 2 per cent, clotting time, forty-five minutes, and blood type, no 2 (Jansky).

November 10 The laboratory examination on this date revealed 2,800,000 red blood cells and 35 per cent hemoglobin. The Wassermann reaction of the blood was negative, and repeated examinations of the urine gave negative results. The average blood pressure was 140 systolic and 90 diastolic. The average temperature during the patient's stay in the hospital was normal. The average pulse rate was 90.

The patient was kept under observation in the hospital for forty-five days. The week preceding admission she received 0.09 Gm of cevitic acid a day by mouth. During her stay in the hospital she received 0.1 Gm intravenously daily, with the exception noted on chart 6. The patient was considered throughout her stay as having thrombocytopenic purpura haemorrhagica idiopathica.

We were anxious to determine whether cevitic acid would have any effect on the course of her condition. At first there appeared to be marked improvement. The purpuric spots disappeared, the bleeding stopped from both the nose and the mouth and the capillary fragility test showed a marked decrease in the number of petechiae. Platelets, however, showed no definite changes which could be associated with these evidences of improvement, the count never rising above 90,000. It should be pointed out that while the patient did not receive a diet high in vitamin except for vitamin C, she was leading a much more protected life in bed.

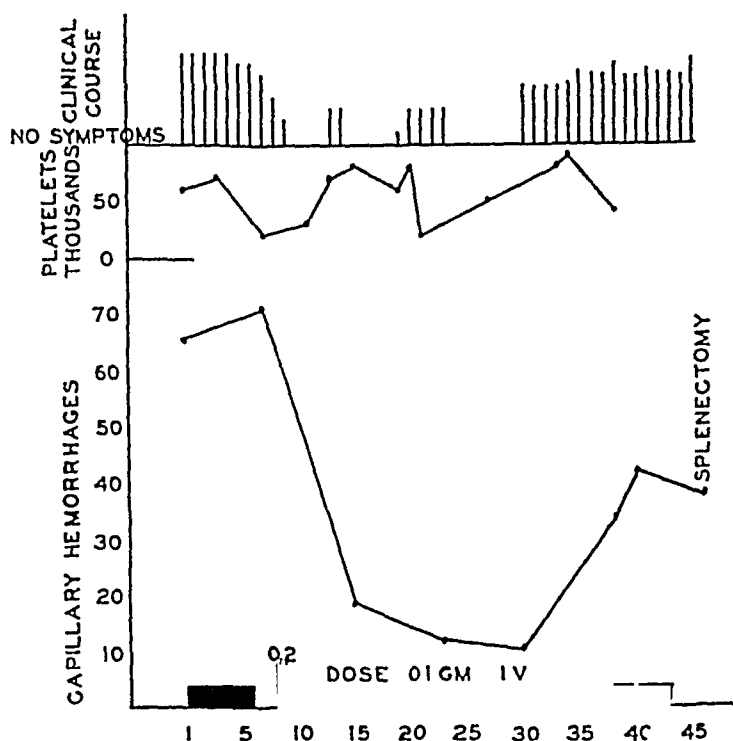


Chart 6—The effect of cevitic acid on patient M G

in the hospital ward than she had been at home, where she had the care of four young children. If we had stopped our experiment at the end of four weeks we might have been inclined to conclude that she was definitely improved as a result of the use of cevitic acid. The value of continued observation is, however, forcibly demonstrated, for it is well known that this type of patient is subject to remissions, and on the thirtieth day she began to suffer from a relapse. From that time on bleeding from the gums, nose and cervix and the subcutaneous bleeding gradually increased. The blood studies at this time showed the following: red blood cells, 4,080,000, hemoglobin, 54 per cent, color index, 0.66, white blood cells, 6,800, polymorphonuclears, 54 per cent (bands, 5 per cent), lymphocytes, 35 per cent, monocytes, 5 per cent, and basophils, 1 per cent. A smear showed hypochromia, polychromatophilia, anisocytosis, poikilocytosis and occasional stippled red blood cells, but no nucleated red blood cells. The coagulation time (Howell) was twelve minutes, the clotting time, nine and a half minutes, the bleeding time, approximately one hour. No clot retraction occurred in five days.

The relapse occurred while the patient was receiving 0.1 Gm of cevitamic acid intravenously daily. On the forty-sixth day she was subjected to a splenectomy. Unfortunately, bronchopneumonia developed and she died.

CASE 2—R. D., a boy aged 2 years and 11 months, was first seen on Nov. 14, 1934, ten days preceding admission to the hospital. It was noticed that following slight trauma large ecchymotic spots appeared at the point of impact. These contrasted with the previous history of the child, which showed that rather severe injury resulted in very slight if any discoloration of the skin. There was no family history of bleeders. Physical examination gave negative results, except for scattered purpuric spots over the body and extremities. The platelet count, taken daily throughout his stay (three weeks), ranged between 110,000 and 40,000. He was given cevitamic acid intravenously, 0.1 Gm daily. During the period of this administration the capillary fragility showed an increase from 15 to 24 petechiae (in a fifteen minute test). The albumin content of the serum was noted to decrease from 5.6 to 4.7 mg per hundred cubic centimeters during the period of administration. The clot retraction time varied from thirteen minutes to two hours and twenty-three minutes, the final time being fifty-five minutes. The coagulation time varied from two and a half to ten minutes, the final time being five minutes. The determination of erythrocytes, hemoglobin and leukocytes showed no significant changes which could be considered due to the cevitamic acid.

*Comment*—This child is apparently suffering from thrombocytopenic purpura haemorrhagica. During confinement to bed the purpuric spots cleared up, possibly owing to the lack of trauma. On the other hand, the capillary fragility test showed a slight increase rather than a decrease in the number of petechiae. The decrease in the amount of serum albumin is also worthy of note. When the patient was allowed to be up a few new purpuric spots appeared. We do not feel that the administration of cevitamic acid had a favorable effect on the course of this patient's illness.

CASE 3—J. W., a boy aged 6½ years, was admitted to the hospital during an interval in a history of repeated episodes of the appearance of purpuric spots and bleeding from the mucous membranes since Dec. 1, 1931. There was no family history of bleeding in this case, and very rarely was a platelet count found to be abnormally low.

Physical examination gave essentially negative results, except for the purpuric spots. The fragility test of the red cells repeatedly gave normal results.

At the time of the present admission the patient was free from symptoms, and only 8 petechiae were found within the circle (fifteen minutes). The patient received 0.1 Gm of cevitamic acid intravenously. During this time, the platelet count varied from 240,000 to 20,000, the last two counts being 20,000 (eleventh day) and 80,000 (fourteenth day), showing a decrease rather than an increase during the time of administration. The capillary fragility changed very slightly, but the last reading was also 8. The serum albumin showed no appreciable change, being 5.1 mg on the third day and 5 mg on the twelfth day of medication. The clot retraction time showed a steady increase from seventeen minutes to one hour and thirty minutes during the treatment. The coagulation time varied from nine minutes to four minutes, the final time being nine minutes. The erythrocytes, hemoglobin and leukocytes showed no significant changes which could be attributed to the cevitamic acid therapy.

*Comment*—As this patient had no symptoms or signs of his purpuric disease at the time of admission, it has been difficult to estimate the action of cevitamic acid in this case. Certainly it did not produce a favorable effect on the platelet count. There was no definite change in the number of petechiae or in the amount of the serum albumin.

We are somewhat at a loss to classify this case satisfactorily, because of the continued high platelet count with very few exceptions during the four years and because of the lack of family history. We feel that the patient must be observed over a much longer period before a definite diagnosis can be established.

#### TRUE HEREDITARY HEMOPHILIA

The last group to be considered is composed of patients with true hereditary hemophilia. As may be seen from chart 7, the two patients showed quite opposite results following the use of cevitamic acid intravenously. Patient M. P. showed a very unsatisfactory result from the point of view of clinical course and capillary fragility, while patient T. N. improved clinically and the capillary fragility became steadily less. Several explanations for this paradoxical picture suggest themselves. One is that these patients were following the normal course of their disease, and one was entering a phase of relapse and the other a state of remission. Another possibility is that the cevitamic acid may have exerted a favorable effect on the patient (T. N.) with true hemophilia only, whereas, in patient M. P., in whom thrombocytopenia had recently developed also, the cevitamic acid failed to exert a favorable influence, just as it failed in the purpuric group.

CASE 1—M. P., a boy aged  $5\frac{1}{2}$  years, was considered to have familial hemophilia. His maternal uncle was known to be a bleeder and died at the age of 18 years of an intestinal hemorrhage. When the patient was 13 months old he fell from his crib and bled severely from the nose. Since that time bruising with minimal trauma had been repeatedly noticed. The first admission to the hospital was for hemarthrosis following a blow to the left knee (May 31, 1932). Treatment was symptomatic. The second admission occurred on May 2, 1934, for tarry stools and acute tonsillitis. On this occasion, in addition to symptomatic therapy there was a transfusion of 350 cc. of whole blood. The third admission, on June 14, was for hormone therapy under Dr. Marshall Pease's supervision. Theelin was administered in large doses, with no noticeable effect. Transfusion had to be employed twice. Pentnucleotide was tried on this occasion, too, but with no result. The physical examination, up to the time of the last admission, had generally given negative results, except for local evidences of hemorrhages, at the joints, nose and lips or subcutaneously.

The history preceding the present admission was as follows. Three weeks after the last discharge from the hospital, the patient bumped his head against a door, and two large hematomas developed and slightly closed black eyes. About two weeks prior to his admission (October 11), the child contracted severe bronchitis, with a temperature of 103 F. and severe anorexia. He had lost 4 pounds

(18 Kg) in weight in the previous two weeks. There was no hematuria or tarry stools. The patient had picked at a scab on his lip three hours before admission, and it was still bleeding.

On physical examination the patient appeared undernourished and underdeveloped and looked chronically ill. There were scattered ecchymoses all over the body. Examination of the head revealed the presence of a few shotty occipital glands. The mucous membranes were pale, the lips bleeding constantly, and the tonsils were enlarged. Shotty cervical glands were present. Examination of the

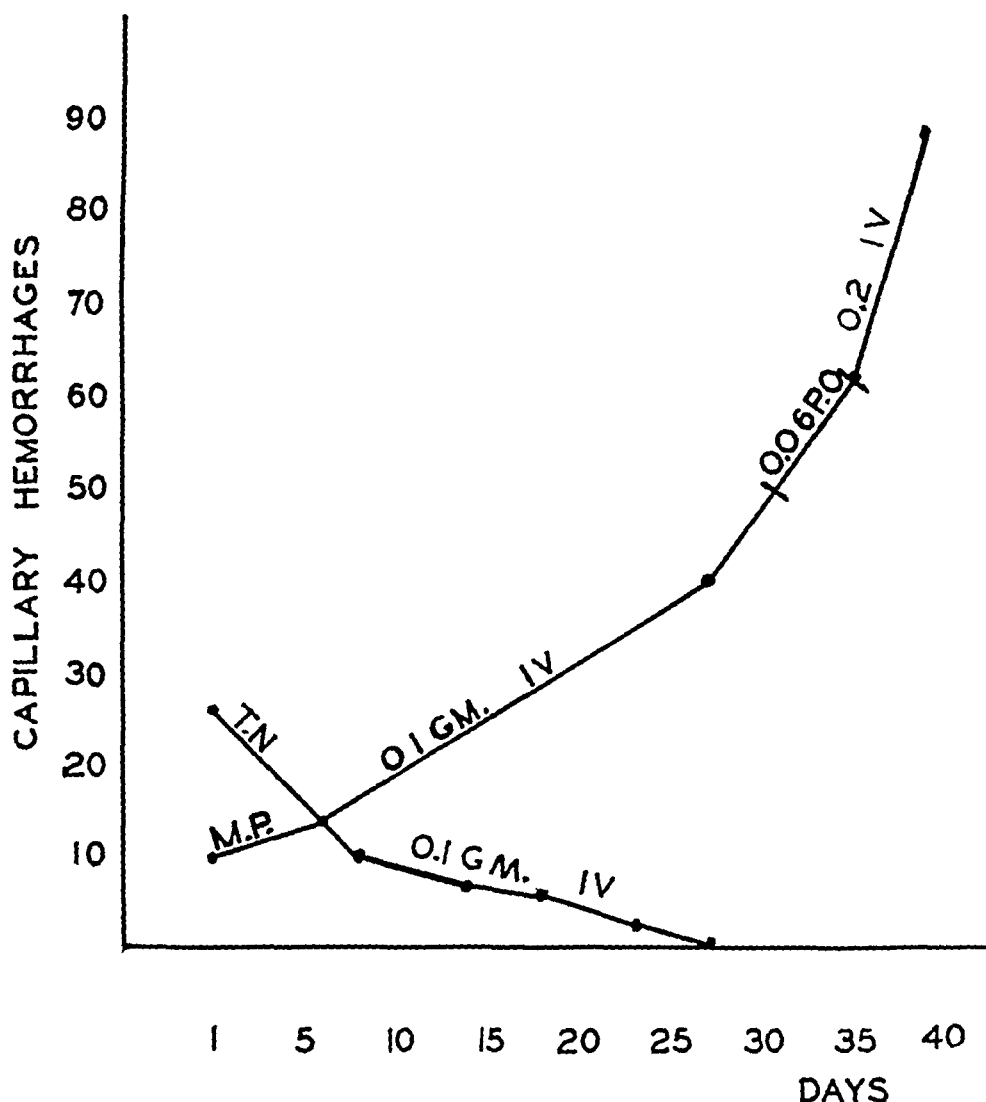


Chart 7—The effect of cevitamic acid on the capillary fragility in two cases of hereditary hemophilia

abdomen showed the spleen to be 2 fingerbreadths below the costal margin in the axillary line and the liver 1 fingerbreadth below the costal margin. Examination of the extremities, except for many ecchymoses, gave negative results. This patient has been followed with fairly frequent blood studies since May 1932. The number of erythrocytes has varied from 1,500,000 to 4,300,000, the final count being 2,420,000. The hemoglobin has varied from 77 to 26 per cent (Sahli), the last reading being 26 per cent. The leukocyte count has varied between 5,200 and 19,800, the last count being 8,400. The differential count has never been significant. The platelet count has been of special interest. At the time of the first admission (1932) three counts were made, the results being 210,000, 220,000 and



255,000, respectively. In July 1934 the boy was admitted to the hospital with a platelet count of 1,500, which rose as follows in three days, to 2,200, in ten days, to 2,600, in seventeen days, to 18,300, in twenty-five days, to 22,500. Numerous platelet counts taken since then have shown a level around 60,000 to 90,000 with one brief, unexplained rise to 170,000, which soon subsided. The final count was 80,000. The bleeding time has varied from nine minutes to ten hours and forty minutes, the final time being three hours. The coagulation time has varied from seven minutes to four hours and fifty minutes, the last time being one hour and twenty minutes. The clot retraction time has varied from one hour to six hours, the last time being one hour and twenty-seven minutes. The standardized tourniquet test was not done on previous admissions, but during the administration of cevitic acid it steadily rose from 10 petechiae to 14, to 40, to 61 and finally to 87 petechiae within the circle (chart 7). The albumin content of the serum increased from 4.4 mg to 4.7 mg during therapy with cevitic acid. The globulin content showed no significant change.

Since the first admission the patient has had a series of treatments with theelin, pentnucleotide and, finally, cevitic acid. Cevitic acid was given as follows: 0.1 Gm intravenously daily for thirty days, 0.06 Gm by mouth for five days and 0.2 Gm intravenously daily for four days. The last blood determinations noted here were made at the end of the cevitic acid therapy. It may be said that the therapy did not appear to influence favorably the findings in the blood or the clinical course to any significant degree.

*Comment*—There are several points of exceptional interest in relation to this patient. He has the family history typical of hemophilia, his hemorrhagic diathesis being transmitted through the mother but found in a male member of a former generation. At the time of his first admission he had a normal platelet count characteristic of hemophilia, but, curiously, since July 1934 the platelet count has always been markedly depressed. He has been treated by various methods, including transfusion, hormone therapy (theelin) and pentnucleotide, with no definite effect. Although it has been reported from Germany that the syndrome of hemophilia has been favorably influenced by the use of cevitic acid, we gave this child 0.1 Gm intravenously for thirty days, 0.06 Gm by mouth for five days and 0.2 Gm intravenously for four days, without demonstrable effect on the clinical course. The capillary fragility increased steadily from 10 to 87. We must therefore conclude that in this case at least cevitic acid did not exert a favorable effect on the course of the disease. It may be noted that the albumin content of the serum, which has been reported as being elevated by the administration of cevitic acid, was 4.2 mg per hundred cubic centimeters on Nov. 24, 1934, 4.4 mg on December 7, and 4.7 mg on December 17.

CASE 2—T. N., a boy aged 6 years, represents the second instance of familial hemophilia in our series, the patient's maternal uncle, aged 33, being a known bleeder. The patient had a marked tendency to bleed from the mucous membranes and to bruise easily since the age of 1 year. The boy had been frequently readmitted to the New York Post-Graduate Medical School and Hospital during the previous two years with episodes of bleeding. At the time of this admission

he showed extensive ecchymoses of the extremities, the spleen was just palpable. He had a large tender swelling on the right side from the groin to the costal margin. He had previously been treated by transfusions and ovarian extract without demonstrable effect. He received cevitic acid, 0.1 Gm intravenously for one week. During this total time the capillary fragility test showed a steady reduction from 25 petechiae in fifteen minutes to 1 petechia in the same time.

The number of erythrocytes during treatment with cevitic acid varied from 4,010,000 to 3,150,000 (last count). The hemoglobin content varied from 78 to 60 per cent (last count). The number of leukocytes varied from 4,700 to 8,850 (last count). The differential count was normal. The platelet count varied from 118,000 to 280,000 (last count). The coagulation time varied from ten minutes to five hours and fifteen minutes, the last time being twenty minutes. The clot retraction time varied from two hours and twenty minutes to twenty minutes, the last time being sixty-one minutes. None of these findings showed a definite curve of either improvement or retrogression. The serum albumin, determined on the second day of treatment, was 5.5 mg, on the twenty-ninth day it was 4.3 mg per hundred cubic centimeters, an actual reduction during treatment. On the twelfth day of treatment otitis media developed on the right side, for which myringotomy was done. At that time treatment with cevitic acid was omitted for five days. At the end of the five days a transfusion of 300 cc was given. The clinical course showed definite improvement during the patient's stay in the hospital.

*Comment*—This patient showed a more favorable course during the period of therapy with cevitic acid. The purpuric spots cleared up, and the increased capillary fragility returned to normal. There was no demonstrable effect on the platelet count. The serum albumin content actually decreased during the therapy, a fact which would tend to indicate that in this type of case it is not essential, as has been suggested by foreign workers, for the amount of serum albumin to increase in order to produce favorable effects on the bleeding. Another point of interest is the fact that a definite infection developed during the time that the child was receiving large doses of cevitic acid, thus demonstrating that this therapeutic agent was evidently not of sufficient value in this regard to protect the patient from an active infection, although the factors of reduced general resistance and overwhelming infection must be considered. Following the clinical course of this patient through this single episode, one might be inclined to conclude that cevitic acid exerted a favorable effect on hemophilia. We know, however, that many spontaneous remissions occur in these cases, and in view of the report of the first case in this series (hemophilia), we must entertain a very decided skepticism as to the real value of cevitic acid in cases of this disease.

CASE 3—J. V., a boy aged 28 months, had been seen repeatedly in various hospitals and after study a diagnosis of hemophilia was always made, although the family history revealed no other bleeders. From the age of 3 months the child had showed an abnormal tendency to hemorrhage or to bruise from the slightest trauma. He had repeated epistaxis and hematuria and purpuric spots, all of which were unaffected by therapy. He had always received a liberal amount of

citrus fruit juices In June 1933 hemarthrosis of the left knee developed In June and July 1933 he received ovarian extract, 4 Gm daily, for three weeks, without effect At that time, the tuberculin, Schick and Wassermann tests were negative In August 1933 the right knee and thigh became markedly swollen, tender and painful on motion They were neither red nor discolored The child had received a series of injections of whole blood into the buttocks (the exact number is not known) with no effect and had begun to receive injections of theelin, 0.5 cc intramuscularly, twice a week, several weeks preceding this episode He was readmitted to the hospital on Aug 3, 1933, with many ecchymotic spots on the abdomen, extremities and scrotum, from 2 to 5 cm in diameter The right knee was twice the normal size, painful, tense and held flexed It was not discolored A roentgenogram showed no evidence of destruction of the bones or epiphysis From the time of admission until October 30 (twelve and one-half weeks) he received 1 cc of theelin twice a week intramuscularly and calcium lactate, 5 grains (0.324 Gm), three times a day orally Throughout this time there was no consistent change in the clinical picture There were recurrent epistaxes, ecchymoses and exacerbation of the hemarthrosis of the right knee, which was in a cast most of the time The left knee continued to be held in a semiflexed position and was painful to move, although there were no exacerbations The patient was discharged on October 30 He was followed in the clinic, showed no improvement and was readmitted to the hospital on Oct 30, 1934, for therapy with cevitic acid He was given twelve doses of 0.1 Gm intravenously and took 3 tablets of 0.01 Gm by mouth for fourteen days This series was given over a period of fifty days Clinically, there was a very marked improvement The ecchymoses and epistaxis ceased, and both joints cleared up entirely, so that he was able to walk and to run for the first time in his two years under observation This improvement has been maintained until the time of writing (one month later) During his period of observation (two years) the blood picture has fluctuated somewhat but without showing apparent response to any therapeutic agent, including the cevitic acid The erythrocyte count has varied from 2,800,000 to 5,000,000, the last count being 4,200,000 (after cevitic acid therapy) The hemoglobin content has varied between 46 and 83 per cent, the last value being 74 per cent The leukocyte count has varied between 6,100 and 14,500, the last count being 9,000 The differential count has not been significant The platelet count has varied from 173,000 to 420,000, the last count being 420,000 The coagulation time has varied from twenty-four minutes to four minutes, the last time being eleven minutes The bleeding time has varied from four and a half minutes to immediately, the last time being half a minute

The capillary fragility was studied during the period of therapy with cevitic acid, and these results were obtained: controls, from 15 to 16 petechiae (seven and a half minutes), third day, 14 petechiae, sixth day, 8 petechiae, eighth day, 7 petechiae, tenth and eleventh days, 8 petechiae, fourteenth day, 17 petechiae, twenty-seventh day, 12 petechiae, thirty-seventh day, 12 petechiae, thirty-eighth day, 8 petechiae, forty-fourth day, 10 petechiae, and forty-ninth day, 8 petechiae Because we are not convinced that familial hemophilia is the correct diagnosis, these readings are intentionally omitted from chart 7

*Comment*—This case is especially interesting because the symptoms might well fit the picture of hemophilia, but there is no family history of bleeding There was a consistently normal or high platelet count The patient had always used a plentiful amount of citrus fruit juice He was under the care of the same physician for over two years and

received a variety of treatments without effect. Cevitamic acid, given intravenously and by mouth, produced a prompt remission of symptoms. It was planned to give this only intravenously, but the veins had been so mutilated by previous intravenous work that daily injections were impracticable. It is possible, however, that the intravenously administered cevitamic acid only was effective, and that we are dealing with one of the group of persons who are unable to utilize vitamin C, even though the oral intake is theoretically adequate.

An almost exact replica of this case has been studied by Dr. Baiber of Alexandria, La. In a personal communication, he reported the same type of encouraging results with the use of cevitamic acid intravenously. There was, however, a relapse with a return of subcutaneous hemorrhages and hemarthrosis when the patient was given cevitamic acid orally.

Three patients with aplastic anemia with profound hemorrhages have been treated with cevitamic acid intravenously, without apparent effect. All three cases terminated fatally.

#### COMMENT

It was to be expected that our findings would differ in some respects from those of the foreign observers previously cited, as their reports were on very small groups of cases. We studied the serum proteins in four of our cases during treatment, and while our readings agree with those of Boger and Schroeder in that the changes in the amount of serum globulin were of no significance, three of the four cases showed a decrease in the amount of serum albumin. This is contrary to their findings of a definite increase in the serum albumin content in patients with hemorrhagic conditions and also in normal persons during cevitamic acid therapy. The first patient in our group presented a typical thrombocytopenic blood picture and showed a decrease of the serum albumin content from 5.6 to 4.7 mg, the second had purpura of an indeterminate type and showed an inconsequential decrease from 5.1 to 5 mg, the third had familial hemophilia and showed an increase from 4.2 to 4.7 mg, and the fourth also had familial hemophilia and showed a decrease from 5.5 to 4.3 mg. These patients were receiving a daily dose of cevitamic acid of from 0.1 to 0.2 Gm intravenously (with rare omissions for various reasons), and they were observed not less than sixteen days, the longest period being forty days. It is therefore evident that an increase in the amount of serum albumin does not always follow therapy with cevitamic acid.

Although a large percentage of our patients were studied for all or part of the blood findings (bleeding time, clot retraction, coagulation time, platelet count and leukocyte count, including a study of the distribution), the results following cevitamic acid therapy were considered

neither uniform nor significant enough to warrant either conclusions of value or their detailed inclusion in this report. The red blood cell count and the hemoglobin content tended to show a slight, consistent rise in the cases of vitamin C deficiency but not in the other groups of cases.

It was interesting to note that while this, like all other vitamins, has been suggested as a preventive for infections of the upper respiratory tract, in one of our patients (with hemophilia) sore throat and otitis media developed for which myringotomy was performed during the time he was receiving 0.1 Gm. of cevitamic acid intravenously each day. The factors of overwhelming infection and reduced resistance, might, however, be considered as outweighing such an influence in any individual case. We feel therefore, that a deferred conclusion as to the value of the substance in the treatment of conditions not due to vitamin C deficiency is justified at this time.

In view of our results and the reports of others it is felt however, that cevitamic acid has been demonstrated to be of great value in cases of scurvy and allied conditions dependent on vitamin C deficiency. It is true that frank scurvy is relatively rare in adults, although as has been already pointed out even some of these cases are not recognized. We do not feel that early or "subclinical" scurvy is a rare disease, even in a large center of civilization. The only symptom may be bleeding gums frequently diagnosed as pyorrhea. In addition to our own experience which has been revealed in the number of cases recognized since we became "scurvy conscious" it has been the experience of many of our associates that they too, began to see more of these patients after their attention had been recalled to this syndrome. In this era of poverty and unbalanced faddists' diets, this group is probably on the increase. In addition, there is the large group represented by those on fruit-free diets because of ulcer, colitis or urticarial treatment, in whom "subclinical" or even frank scurvy may develop. Schultz<sup>47</sup> obtained interesting results as follows. Nine of eighteen patients with ulcer with normal capillary resistance, after having been on a diet deficient in vitamin C for about sixteen days showed lowered capillary resistance, another series of seventeen patients confirmed this result, not all showed lowered resistance because of the different length of time required to produce the syndrome in different persons, in five patients the capillary resistance was restored to normal by the addition of vitamin C (tablets of pulverized dog rose berries, not cevitamic acid), in two cases this result could not be obtained. Schultz<sup>48</sup> did not, however, express the belief that C avitaminosis is an etiologic factor in the production of gastric ulcer.<sup>18</sup>

47 Schultz, P. Hospitalstid **77** 1052 (Sept 25) 1934, abstr., J. A. M. A **103** 1998 (Dec 22) 1934.

48 Schultz, P. Hospitalstid **77** 1190 (Oct 30) 1934.

To this whole scorbutic group cevitic acid would seem to be of value, especially to those who, for whatever reason cannot or will not take fruit juices. Under our guidance it has been tolerated when taken by mouth in five cases of gastric or duodenal ulcer during the acute posthemorrhagic phase (one of these is reported here). Seven patients with ulcerative colitis have taken it by mouth without any evidence of intestinal irritation. Two adult patients who were forbidden citrus fruits because of sensitivity have been able to take it without untoward symptoms. We have administered it with excellent results to two infants who could not tolerate citrus fruit juice. We feel that all patients on a diet poor in vitamin C should be given cevitic acid as a protective measure, unless a specific contraindication should arise.

It should be pointed out that several patients who proved to have scurvy on the basis of careful dietary history, physical signs, clinical development, capillary fragility and response to vitamin C, had previously, because the blood picture was not typical of a specific purpura, been considered to have purpura of an undetermined type. Probably many more instances of this syndrome are wrongly diagnosed.

The question of dosage cannot be completely answered on the basis of the limited total experience with this substance. In our series a patient with extremely severe scurvy was cured by the use of 0.06 Gm of cevitic acid daily by mouth. The patient with the next most severe condition seemed to require 0.09 Gm daily by mouth. To a third patient we gave as high as 0.12 Gm by mouth daily. This patient had a digestive upset on the second day, with nausea and diarrhea. Although no other cause could be found for this upset it is questionable whether the cevitic acid was responsible, because the same patient started to take 0.12 Gm a few days later and was able to continue without any signs of gastro-intestinal distress.

Although a few former workers have given over 100 mg a day or from 150 to 200 mg every other day intravenously, we gave four of our patients 200 mg a day intravenously, one for as long a time as fourteen days. These patients were all children and weighed 60 pounds (27.2 Kg) or less. No injection in our entire series ever produced any evidence of a reaction. Because we are dealing with a substance which is destroyed by heat and hence cannot be completely sterilized, this phenomenon is all the more interesting. We have dissolved the contents of a vial (100 mg) in from 5 to 10 cc of sterile distilled water or sterile physiologic solution of sodium chloride and injected it slowly. We have not determined what the maximum tolerated dose will be or what the effects of actual overdosage would be.<sup>49</sup> Certainly, the range

<sup>49</sup> We have since administered 1,000 mg intravenously daily for periods of fourteen days and 2,000 mg intravenously on several occasions without untoward effects.

between the therapeutic and the toxic dose is very wide. The present substance is irritating if injected into the tissues, but a newly modified preparation is reported to be suitable for such use. The present preparation may be used subcutaneously or intramuscularly if the following technic is utilized. Dissolve the cevitic acid in sterile water and neutralize with one-half its quantity of sodium bicarbonate (yielding a solution about  $pH$  7). The dissolving and neutralizing should be done immediately before administration to avoid loss of effectiveness.<sup>50</sup>

The minimum dose of cevitic acid required as a preventive has yet to be determined. At present, it seems that from 20 to 30 mg should be adequate. Probably considerably less will prove sufficient. No laboratory or physical finding has been nearly as helpful in following the clinical course of this group of patients as the capillary fragility test standardized as described.

#### CONCLUSIONS

A crystalline substance, cevitic acid, has been identified, isolated and synthesized. It is identical with crystalline vitamin C.

This substance has proved to be of great value in the treatment of scurvy and other evidence of vitamin C deficiency.

Its value in the treatment of thrombocytopenic purpura or familial hemophilia is doubtful.

Further studies will be necessary to evaluate its status in the treatment of many other conditions which have been reported as favorably influenced by this substance.

A standardized modification of the tourniquet test for capillary fragility, which has been found most useful in the study of these cases, is presented.

Cevitic acid can be used safely for patients with gastric or duodenal ulcers and patients with severe ulcerative colitis.

Cevitic acid can be used by certain patients who are unable to take citrus fruit juices because of sensitivity and by certain infants who cannot tolerate citrus fruit juices.

Cevitic acid should be added to all diets poor in vitamin C as a preventive.

Many cases of early and "subclinical" scurvy are not recognized.

There are two groups of these patients: those whose intake of vitamin C is inadequate and those who are unable to utilize vitamin C even though the intake is adequate.

The latter group may, for the most part, be successfully treated by cevitic acid administered parenterally.

Dosage, tolerance and methods of administration have been discussed.

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<sup>50</sup> Fisher, B. H., and Leake, C. D. The Parenteral Administration of Cevitic Acid (Ascorbic Acid) Solutions, *J. A. M. A.* **103**: 1556 (Nov. 17) 1934.

# ADRENAL INSUFFICIENCY RESULTING FROM PARTIAL OR TOTAL ATROPHY OF THE ADRENAL GLANDS

## EARLY CLINICAL RECOGNITION

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Disturbances in adrienal function have thus far been recognized only at relatively late stages. The reason for this apparently is twofold. First, Wilks'<sup>1</sup> paper, in which he rearranged and reclassified the cases on which Addison's<sup>2</sup> original report was based, excludes all but those cases which can be placed in a very limited category. For instance, Wilks did not accept cases without pigmentation or without tuberculosis of the adrenal glands as being instances of Addison's disease. Thus he influenced adversely the recognition and diagnosis of partial adrenal insufficiency by the elimination of all cases but those with clearcut symptoms.

A second reason is that adrienal insufficiency, although constantly present to a degree, is openly manifest only at intervals over a given period of years. Thus patients suffering from this disease receive an array of diagnoses, some of which are erroneous but all of which detract from adequate study of the underlying disturbance. Accordingly, rather than progressively earlier recognition, the diagnosis continually is made in the late, terminal stages only.

It is thus with emphasis on the feasibility of early clinical recognition of the lesser degrees of adrenal insufficiency that the material contained herein is presented.

## REVIEW OF THE LITERATURE

The fact that cases of adrenal insufficiency which satisfy the strict criteria established by Addison and Wilks represent only one of the many possible varieties is emphasized in both early and recent literature. Wilks, for instance, in 1862 stated that "Doctor Addison was impressed with the belief that the constitutional symptoms existed long before the

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1 Wilks, S. On Disease of the Supra-Renal Capsules or Morbus Addisonii, Guy's Hosp. Rep. 8 1, 1862.

2 Addison, Thomas. On the Constitutional and Local Effects of Disease of the Suprarenal Capsules. London: S. Highley, 1855.



discoloration of the skin" Indeed, "he was led to the fact of certain patients dying without discoloration, in whom the changes of the morbid material of the capsules had not reached that final degree which is sometimes met with'

Rowntree<sup>3</sup> and others indicated the possibility of the existence of early manifestations in their recognition of a "period of initial destruction of the suprarenal glands" They did not ascribe definite symptoms to this period but stated that the symptoms of asthenia, pigmentation and loss of weight and strength mark the onset of the second stage, namely, the one in which the functional activity of the adrenals is insufficient for the daily physiologic requirements In contrast to this, it is my belief that many characteristic symptoms are presented by patients in the interval between the onset of the destructive processes in the adrenals and this "second period," which later appears to be rather the initiation of the terminal stage

The existence of early clinical indications of adrenal insufficiency is substantiated by certain case reports In Brenner's<sup>4</sup> first case, the symptoms undoubtedly associated with adrenal insufficiency (as interpreted with respect to the behavior of our patients) were responsible for an appendectomy at the age of 28 years for "chronic appendicitis," "pneumonia" at 29 and 'gastric influenza' a year later, not long before death occurred from disease of the adrenal glands In Brenner's second case the patient had dyspepsia with occasional vomiting steady loss of strength and increased pigmentation following a severe mental shock one year previously The patient became weaker and more bronzed over a period of two years, with attacks of abdominal pain later in the disease In Wells' fourth case the patient 51 years old at the time of her death, had been under observation for more than four years The onset of the symptoms followed a strict regimen attendant on an attempt to lose weight Brown spots on the legs and asthenia soon occurred and, together with low blood pressure, continued practically unchanged in spite of treatment until her death Pain between the shoulder blades was a prominent feature at one time

A discordant note regarding the correctness of the diagnosis, even in the face of the classic symptoms of Addison's disease, is struck by Harrop,<sup>6</sup> who obtained atypical clinical response to treatment with

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3 Rowntree, L. G., and Snell, A. M. A Clinical Study of Addison's Disease, Mayo Clinic Monographs, Philadelphia, W. B. Saunders Company, 1931

4 Brenner, O. Addison's Disease with Atrophy of the Cortex of the Suprarenals, *Quart J Med* **22** 121, 1928

5 Wells, H. G. Addison's Disease with Selective Destruction of the Suprarenal Cortex, *Arch Path* **10** 499 (Oct.) 1930

6 Harrop, G. A., Weinstein, A., Soffer, L. I., and Trescher, J. H. The Diagnosis and Treatment of Addison's Disease, *J. A. M. A* **100** 1850 (June 10) 1933

adrenal cortex extract The excellent results of Haitman,<sup>7</sup> however, even in the cases apparently not of gross adrenal involvement, would make one suspect that failure to obtain results was caused by use of an impotent extract

Experimental work with the adrenal glands of animals confirms the impression from clinical sources that minor degrees of adrenal insufficiency are recognizable from the symptomatology Hartman, for instance, reported that lesser degrees of adrenal insufficiency, produced by the maintenance of adrenalectomized cats on insufficient doses of cortical hormone, cause such symptoms as gradual loss of weight, decrease in resistance to cold and more ready fatigability Laboratory studies reveal correspondingly slight but definite changes In rats with chronic adrenal insufficiency but with no marked symptoms, Wyman and Walker<sup>8</sup> reported that the blood sugar content was maintained at a low level of the normal average, occasionally dropping below the normal Geiling and Britton reported a fourfold susceptibility to insulin in rats with chronic adrenal insufficiency with no increase in blood sugar following hypoglycemic convulsions produced by insulin Swingle and others<sup>9</sup> reported an increase in phosphorus, protein, nonprotein nitrogen and urea and a decrease of sugar in the blood of adrenalectomized cats

Thus, even though the majority of the early symptoms are those usually associated with clinical conditions bordering on functional diseases, it is believed that their proper evaluation provides the means for the clinical recognition of partial and total adrenal insufficiency

#### REPORT OF CASES

The case reports are presented in detail not only to stress the varied early manifestations of the disease but to provide an adequate basis on which a description of its early symptomatology may be built

CASE 1—A G was first admitted to the Boston Psychopathic Hospital on Feb 9, 1925, at the age of 20 At that time the past history revealed that he had been very ill at the age of 6 months with a questionable gastro-intestinal disturbance A discharge from an ear, which began in early childhood, continued until he was 18 He had diphtheria at the age of 4 or 5 years As regards his personal history, he remained alone for the most part, having only an occasional friend and never mingling with any of his brothers' or sisters' friends

The immediate reason for his admission to the hospital was an illness characterized by fever, rapid respiration and incontinence of urine and feces He

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7 Hartman, F A Studies on the Function and Clinical Use of Cortin, *Ann Int Med* **7** 6, 1933

8 Wyman, L C, and Walker, B S Studies on Suprarenal Insufficiency, Blood Sugar in Suprarenalectomized Rats, *Am J Physiol* **89** 215, 1929

9 Swingle, W W Blood Changes Following Bilateral Epinephrectomy in Cats, *Am J Physiol* **79** 666, 1927 Swingle, W W, and Pfiffner, J J Adrenal Cortical Hormone, *Medicine* **11** 371, 1932

neither answered questions nor cooperated in any way with the examining physician. He was apparently conscious but confused. The opinion of the physician who saw him before admission to the hospital was that his was "an acute illness of the encephalitis type."

Physical examination on admission to the hospital revealed a flushed, stuporous, almost comatose white youth with rapid pulse and respiration. The pupils were slightly irregular but reacted fairly well to light. The eyes were turned to the left but did not oscillate. The right tympanic membrane was red and crusted. The Kernig sign was negative, the neck was not stiff. The left arm and leg were flexed, and the head was turned to the left. Deep and superficial reflexes were absent. The pubic hair was of feminine distribution. The blood pressure was 110 systolic and 70 diastolic.

The urine was normal. The white blood cell count ranged between 8,000 and 14,000 cells per cubic millimeter. The temperature reached a maximum of 102 F daily. Examination of the cerebrospinal fluid on Feb. 10, 1925, revealed 5 lymphocytes, the test for globulin gave negative results, sugar content was 330 mg per hundred cubic centimeters of fluid, the total protein, 18 Gm per liter, and the colloidal gold curve negative. The Wassermann reactions of the blood and spinal fluid were negative. A blood culture taken on admission was reported negative on the ninth day. A Widal test gave negative results on February 10. A series of determinations of blood sugar gave results as follows:

	Blood Sugar Mg per 100 cc	Comment
February 11	52	Fasting
12	167	After administration of dextrose for 18 hours
13	86	Fasting
14	74	Fasting
15	89	Fasting
18	103	Fasting

A determination of the mental status was made several days after the patient's admission. He lay quietly in bed, taking little interest in his environment, he initiated very little talk but was coherent and relevant, his mood was stable, he had no delusions, hallucinations or compulsions, he was partially oriented, he showed amnesia for the period from Sunday night to Wednesday afternoon, his grasp of general information was only fair, his judgment and insight were questionable.

On February 14 it was noted that the knee jerks were elicited when re-enforced. There was still the question of a Babinski sign on the right side. The face seemed weaker on the right. The chest showed rough, harsh sounds throughout. The patient complained at times of abdominal pain, but physical examination of the abdomen never revealed any abnormalities. Except for clearing of the drowsiness, the patient's condition was approximately the same after ten days as on admission, the temperature curve in particular having shown no change. Despite this, the patient was sent home at that time on the insistence of the family. It was the opinion of the members of the staff who saw the patient that encephalitis had developed in defective cerebral tissue.

Admission of the patient to the Peter Bent Brigham Hospital in April 1927 was occasioned by fever and malaise of five days' duration. A review of the history revealed that he was subject to frequent headaches and had changed glasses several times in the preceding few years because of this. Objects were seen

well close at hand but only with difficulty at distance. There were frequent colds with hacking cough but very little sputum. The illness responsible for the admission began five days previously. After twenty-four hours in bed, following a chilly sensation and a feeling of malaise, the patient got up but was still feeling weak. The cough which he had had at intervals previously returned, together with the headaches, thus necessitating his return to bed. Four days before admission to the hospital he first noted dull, steady pain over the whole abdomen generally but particularly severe below the umbilicus. Throughout this portion of his illness the pulse rate remained about 85, while the temperature reached a level as high as 102.5 F.

Physical examination showed that the pupils were equal and regular and reacted to light and in accommodation. Ophthalmoscopic examination revealed normally colored disks, which were well outlined except for the superior nasal quadrant of the right disk, which was somewhat hazy. An inconstant diastolic thrill and murmur were present over the precordium. The blood pressure was 95 systolic and 50 diastolic. The lungs were essentially clear except for harsh breath sounds near the midline on either side posteriorly. There was slight tenderness to pressure all over the abdomen below the level of the umbilicus, no organs were palpable. Gross neurologic examination gave negative results. On May 1 the blood pressure was 70 systolic and 50 diastolic.

The laboratory findings were hemoglobin, 90 per cent (Dare), erythrocytes, 4,900,000, leukocytes, 8,300, blood smear, normal. The leukocyte count subsequently remained at about 10,000. The urine was normal except for the slightest possible trace of albumin in the twenty-four hour specimen. The Wassermann reaction of the blood was negative. Agglutination tests for typhoid and paratyphoid A and B organisms were negative on April 24 and May 2, two blood cultures at corresponding times gave negative results. No tubercle bacilli were found in the sputum. An electrocardiogram showed normal curves.

The patient's temperature reached normal on the tenth day of his stay in the hospital. A roentgenogram of the chest taken on May 3 was reported as showing flattening of the right side of the diaphragm, with an indistinct costophrenic angle on the right. There was diffuse mottling of the base of the right lung, but the lungs elsewhere were apparently normal. Following the return of the patient's temperature to normal, convalescence was rapid, so that on the eighteenth day he was discharged.

The third, and last, admission to the hospital was on July 25, 1933, at which time, after approximately eighteen hours in the Peter Bent Brigham Hospital, he died. The chief complaint was weakness. In the interval since the last admission, the patient had remained in fair health but had continued unsocial. There was no evidence of parkinsonism, but for two days prior to his admission there was spasticity of the arms, particularly of the right, together with numbness of the middle, fourth and little fingers of the right hand. There were never any cardiovascular symptoms. The patient had taken iron and liver on occasion for anemia. The present illness began five weeks prior to the patient's admission to the hospital, with the onset of a feeling of warmth and fever. There was some cough with the production of a small amount of whitish sputum. After a short period of rest in bed at home the temperature dropped from 102 F to normal coincident with the clearing up of "moisture," which the patient's physician found in his chest. Several attempts to get out of bed were followed in each instance by a recurrence of the fever and prostration. For several days preceding the admission, the patient had been able to take only liquid foods and had felt weak and cold.

Physical examination on the patient's arrival at the hospital this time revealed a drowsy-appearing white youth. His features were sunken, the skin, smooth and cool. The left arm was markedly spastic, and the forearm was kept flexed at a right angle. The right arm exhibited typical catatonicy. Ophthalmoscopic examination gave negative results. A presystolic rumble was heard at the apex of the heart. Blood pressure was 110 systolic and 70 diastolic. There were occasional crackles audible at the base of each lung. The blood pressure continued to fall with the passing of time, so that nine hours after admission it reached 70 systolic and 40 diastolic, and from several hours later until death it was unrecordable.

Laboratory studies revealed a hemoglobin content of 110 per cent (Sahli), 5,000,000 erythrocytes and 15,000 leukocytes, with an essentially normal differential count except for a preponderance of young polymorphonuclear cells. The urine contained a minimal amount of albumin, occasional leukocytes, 25 red blood cells per high power field and an occasional cast. The Wassermann and Hinton reactions of the blood serum were negative. The blood sugar content six hours after admission was 101 mg per hundred cubic centimeters. Lumbar puncture revealed a low initial pressure of 30 mm of water, a normal response to compression of the jugular vein, 2 cells per cubic millimeter of spinal fluid, negative Wassermann and colloidal gold reactions and a total protein content of 35 Gm per liter.

At autopsy the adrenal glands could not be palpated, the pancreas was approximately normal and the thymus was small. The heart, which weighed 210 Gm, appeared normal except for the mitral valve, this showed slight stenosis, the circumference of the valve measuring 4.2 cm. The lungs on the cut surface showed yellowish nodules from 2 to 3 mm in diameter, scattered throughout the lung tissue but with the majority at the base. The liver, weighing 1,180 Gm, appeared to contain more fat than usual. Two portions of tissue from the region of each adrenal gland were described as possessing very little cortical tissue and a soft, pale, more yellowish type of medullary tissue than usual. No additional adrenal tissue was identified in the usual position. The testes were smaller and softer than normal, each weighing 19 Gm. The thyroid gland was extremely atrophic, weighing only 4.5 Gm but presenting the usual lobes and an isthmus. The two parathyroid glands appeared normal. Examination of both the brain and the spinal cord before and after fixing in solution of formaldehyde revealed no abnormalities.

Microscopic examination of the adrenal glands (fig. 1) showed atypical structures. There was no differentiation into cortex or medulla, instead, embedded in fatty areolar tissue were small collections of cells, the majority of which were vacuolated. Some of the vacuolated cells had increased from two to three times their normal size and contained only a narrow rim of cytoplasm around what was formerly a large vacuole. In other areas, the majority of the cells were fairly well preserved. They were polygonal and contained moderately deeply staining nuclei. The latter were embedded in homogeneous reddish-brown cytoplasm. There were all gradations from cells with small vacuoles to those composed almost entirely of a vacuole, in which case the nucleus, in signet-ring fashion, was pushed against the wall of the cell. The anterior lobe of the pituitary gland contained approximately 3 per cent acidophilic cells, the number of basophils appeared to be increased. The cells extending along the infundibulum were fairly large, swollen and vacuolated. The pineal gland was normal. The thyroid vesicles varied in size. In several areas practically all of them were small and packed with colloid. Elsewhere throughout the gland both small and large ones were in evidence. The colloid in general was normally stained. The epithelium of the acini was

cuboidal and in a few of them presented infoldings. There were numerous collections of lymphocytes throughout the gland, chiefly in the loose connective tissue. In the testes the number of interstitial cells was reduced. Those present showed neither granules nor crystalloids. Differentiation of the remaining elements of the testis had not reached the spermatid stage. The pancreas, spleen, liver and kidneys were normal. The myocardium showed an increase in brown

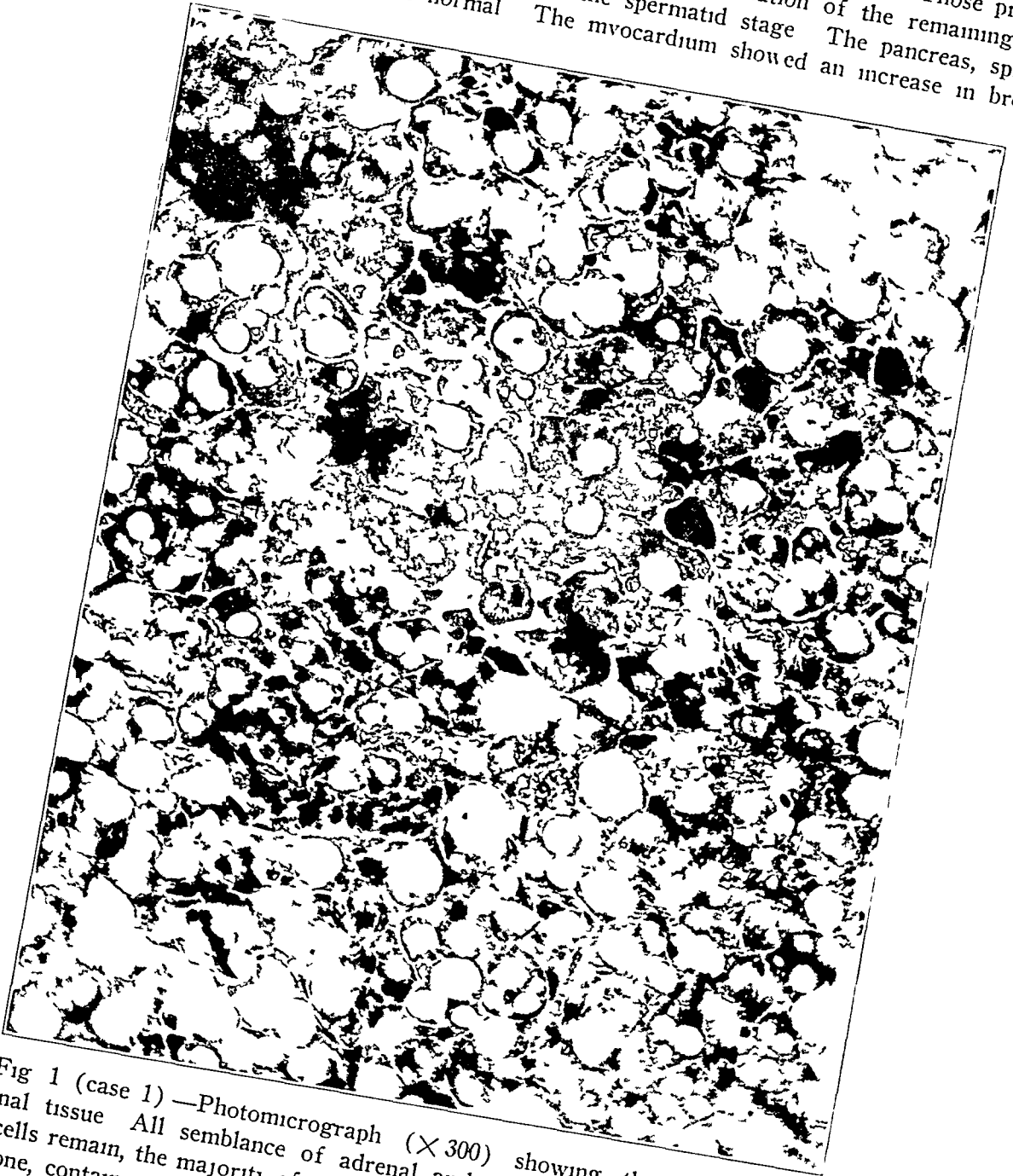


Fig 1 (case 1)—Photomicrograph ( $\times 300$ ) showing the better preserved adrenal tissue. All semblance of adrenal architecture has disappeared. Only a few cells remain, the majority of which contain large vacuoles. A rare area, such as this one, contains a group of such cells.

In some areas of the sections of lung the tissue appeared normal. In others there was obliteration of the normal architecture by loose connective tissue, in which the majority of the cells which contained large fat vacuoles were interspersed with globules of fat lying free in the connective tissue. Many of the

alveoli in the more normal-appearing portions of lung were filled with similar globules. The parathyroid glands, several lymph nodes, the aorta and sections of tissue from the central nervous system were normal. A section of bone marrow showed a diminished number of cells, with the majority of the cells of the myeloid series immature.

CASE 2—M. B. W., a girl 14 years old, was admitted to the Peter Bent Brigham Hospital for the first time in March 1916, complaining of pain in the stomach. The patient had always been in rather poor health. She had measles and chickenpox in childhood, and six months before admission, "pleurisy" in the lower part of the chest on the right side. She became dyspneic on exertion, had a hacking cough with greenish sputum since the preceding summer, was fastidious as regards her diet and ate only certain foods which agreed with her. The morning before admission to the hospital, while on her way to school, the patient was seized with a severe, sharp pain in the right upper quadrant of the abdomen, which was worse on deep inspiration. After ten hours the pain radiated "all over her stomach." The patient had been nauseated since the onset of the attack, and although most of the pain was in the right upper quadrant, appendectomy was performed twenty-four hours after admission. The results of the physical examination were essentially negative. The temperature was 102 F, the blood pressure 102 systolic and 58 diastolic and the leukocyte count 6,000. The appendix was diagnosed as normal after histologic examination.

The second admission to the hospital, the first for medical attention, occurred when the patient was 24 years old. The chief complaint at that time was vomiting. The patient at that time had been married seven years and had borne five children, all of whom were living. The systemic history revealed profuse leukorrhea since the last delivery and normal catamenia since the age of 14. She had been constantly nervous, had fainted when excited, had felt jumpy and had had twitching sensations in the hands and feet since the third delivery. She had lost 20 pounds (9.1 Kg.) during the preceding year. The onset of the present illness followed severe hemorrhages incident to retained placental tissue from her delivery six weeks previously. Uneventful convalescence, after two transfusions, was in turn followed by weakness, fatigue, vertigo and nausea at the sight of food. On physical examination the blood pressure was found to be 100 systolic and 70 diastolic. There was an involuntary twitching motion of the arms and legs, accentuated by calling the patient's attention to it. There was a coarse tremor of the extended fingers. Subsequent determinations of blood pressure one and two weeks after admission were 90 systolic and 70 diastolic and 100 systolic and 70 diastolic, respectively. There was marked subjective improvement following administration of liver and reduced iron. Changes noted in the blood meanwhile were an increase in the hemoglobin content from 60 to 70 per cent (Dare) and in the erythrocyte count from 3,700,000 to 4,400,000. The leukocyte count remained around 7,000, with 40 per cent lymphocytes.

The third admission, which occurred approximately eight months later, was occasioned by vomiting and occipital headaches. The patient meanwhile had been followed in the dispensary, where a loss of 5 pounds (2.3 Kg.) was recorded. The patient then weighed 96 pounds (43.5 Kg.). She had had no menstrual periods since discharge from the hospital. Each month, however, at about time for the menstrual period, the patient would have a spell of vomiting of from one to three days' duration. Until October 1928, the attacks of vomiting were accompanied by chills and fever, but subsequently these disappeared until the patient was admitted to the ward on their recurrence. Examination revealed a poorly developed and malnourished white woman who appeared ill. The pupils

were large and reacted to light and in accommodation. There were photophobia, pallor and blurring of the margins of the disks, with absence of cupping. On admission the blood pressure was 86 systolic and 56 diastolic. There was tenderness on palpation of the abdomen over the aorta, just to the left of the midline. The knee jerks were hyperactive. Two days after admission a strong odor of acetone was noted on her breath. Three days later the blood pressure was 92 systolic and 64 diastolic, the patient meanwhile having become increasingly drowsy, in fact, almost comatose. After a period of fasting the blood sugar content was approximately 44 mg per hundred cubic centimeters of blood. The patient responded well to an injection of 500 cc of a 10 per cent solution of dextrose given by hypodermoclysis and to another injection of a corresponding amount of a 20 per cent solution given intravenously. Two days later (January 10) the blood sugar content after a period of fasting was 50 mg. Subsequent determinations on January 20 and 27 showed 64 and 130 mg, respectively. The blood pressure remained low, namely from 80 to 100 systolic and from 50 to 60 diastolic. The abdominal pain recurred during the week ending February 5. The basal metabolic rate on January 28 and 31 was  $-24$  and  $-32$ , respectively. At the end of two months the patient gradually improved so as to be able to walk unassisted, and she soon left the hospital.

The fourth, and last, admission to the hospital was of short duration. Five and one-half months after her last admission the patient returned because of vomiting. Having been fairly well previously, she began to feel fatigued six days before admission. A fever the next day was followed by nausea, vomiting and frequent severe chills, she "couldn't get warm." The blood pressure on admission was 78 systolic and 46 diastolic. The patient appeared ill and had an area of tenderness to deep pressure over the umbilicus, the abdominal reflexes were absent. The patient's course was gradually downhill, the temperature rose to 106 F, and the blood pressure became unobtainable. The blood sugar content three days before death was 87 mg, the carbon dioxide combining power of the blood plasma was 36.3 per cent. A culture of the blood taken the day before death was negative. Examination of the urine showed a very slight trace of albumin and the slightest possible trace of acetone. The hemoglobin content and the red blood cell count remained approximately at previous levels, namely 60 per cent and 3,700,000.

At autopsy it was noted that hair was practically absent over the axillae and pubes. The breasts, somewhat pigmented, were otherwise not abnormal. There was no evidence of the presence of a thymus gland. The heart was small and the myocardium slightly more brown than usual. The spleen weighed 240 Gm and the pancreas 51 Gm. There was a brownish tinge to the liver. The pelvic organs were normal, as was the brain. A blood culture taken at the time of autopsy was reported negative. The adrenal glands were markedly decreased to about one fifth of the normal size. Both the cortex and the medulla were narrowed, the former to a greater degree.

On microscopic examination, the architecture of the adrenal glands (fig 2) was markedly changed, chiefly in the cortex. The glomerular zone was absent, in its place were many small flattened cells with dark pyknotic nuclei. The arrangement in groups persisted to a degree, but at the periphery nothing more than layers of elongated, dark-staining nuclei were present, and these merged with the surrounding fibrous tissue. The remaining portion of the cortical tissue, which constituted half the bulk of the adrenals, was composed of strands of small, closely packed, more or less polygonal cells. A few areas in this zone contained small adenoma-like structures in which the cells approached a more



normal appearance, that is, they were similar to the cells of the normal zona fasciculata. The polygonal outline of these cells was more readily identifiable, their cytoplasm had the more usual vacuolated appearance, and their nuclei appeared more normal than the remainder of the surrounding cells. The cells of the medulla, markedly decreased in number, appeared normal except for autolysis. The adrenal gland showed practically identical changes except that those in the region of the

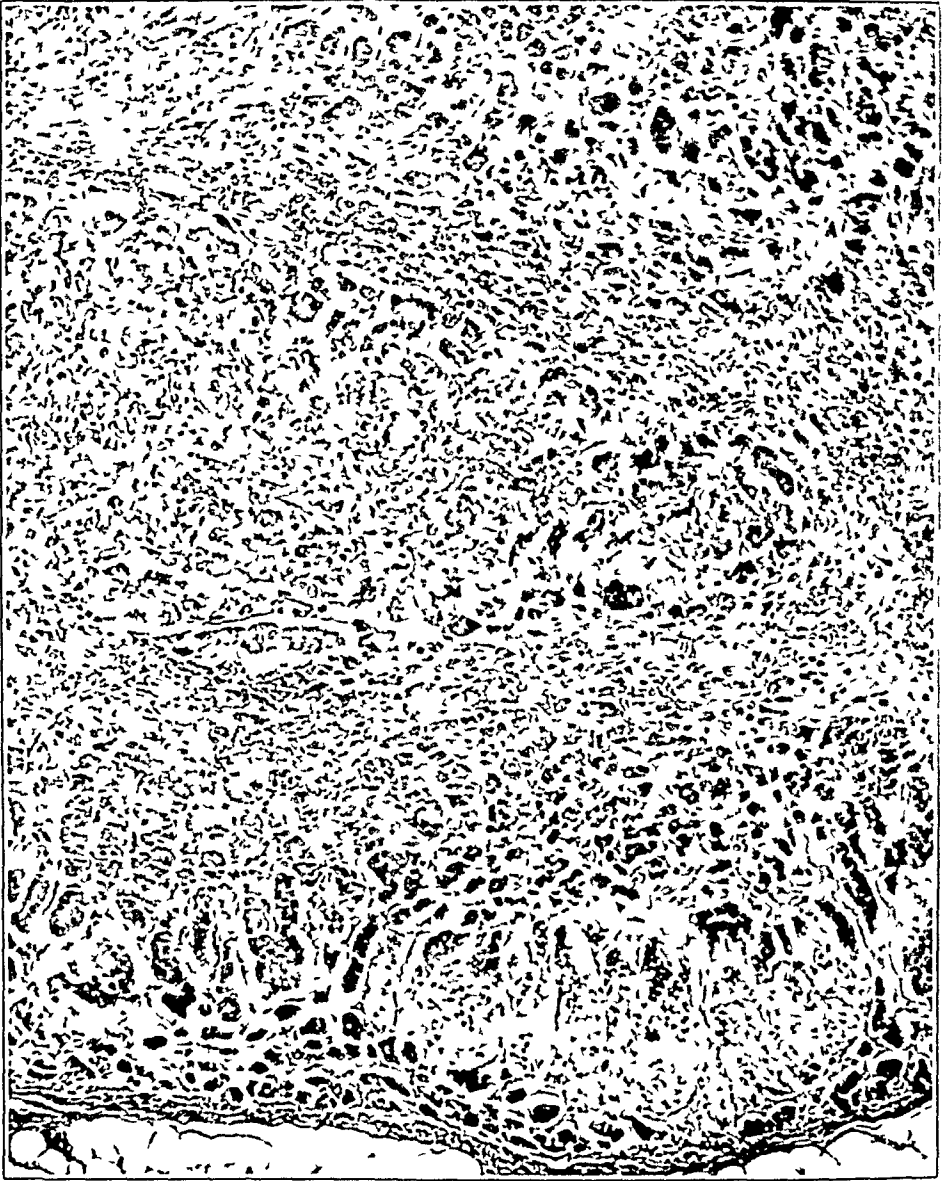


Fig 2 (case 2) —Photomicrograph ( $\times 90$ ) showing that semblances of the normal adrenal architecture are present, while the amount of tissue is markedly decreased. Several small regenerated areas are present.

zona glomerulosa were less marked. The thyroid gland showed areas of varied appearance. In some, the follicles approached normal size and content but were lined with cuboidal epithelium which was lower than normal. In other areas the follicles, practically free from colloid, contained more normal-appearing cells, while those of the walls presented frequent infoldings. In some regions the

connective tissue stroma was markedly increased. There was only slight infiltration with lymphocytes. In the ovary, the follicles were in all stages of development but were markedly reduced in number and embedded in an increased amount of fibrous tissue. There was central necrosis of the liver. The myocardium contained an increased amount of brownish pigment. There were a few patches in the sections of lung indicating very clearly pneumonia, the spleen was normal.

#### COMMENT

The cases here reported exhibit practically every feature recognized thus far, either clinically or experimentally, as an accompaniment of adrenal insufficiency.

Surpassing those cases of adrenal disease due to tuberculosis, in which the average duration is from six months to two years, in our cases symptoms were present over periods of eight and three years respectively. In general, such cases of long duration are characterized by intervals of relatively great freedom from symptoms. One patient in Wells' series, for instance, presented exacerbations and remissions at intervals over a period of four years. Data as to the duration are, however, very probably inaccurate, because if the patient does not happen to be under the care of the physician who saw him in the first stages of the disease, there is great probability that the several disturbances will be interpreted as of different origin.

Addison's term, general languor and debility, best describes the chief symptoms present in our cases. This part of the disability was disturbing and interfered with the well-being of our patients to a marked degree, while in addition it probably accounted for their decreased motor and cerebral activity.

Gastro-intestinal upsets as evidenced by nausea and vomiting, likewise play a significant rôle. For instance, each of the last three admissions to the hospital of our second patient was occasioned by vomiting. Further, during the period between the second and the third admission, the vomiting of the patient occurred at monthly intervals and was associated with expected but never occurring menstruation. This probably resulted from the increase in adrenal insufficiency incident to the added stress of the catamenia, which resulted in a low blood sugar content and vomiting.

Pigmentation in our patients was present only to the extent of a slight yellowish tint to the skin. There was no history or indication of bronzing of the skin. That this is, however, entirely compatible with the presence of adrenal disease is evident from one of the cases described by Wells and a case mentioned by Kaufmann<sup>10</sup>. In fact, certain German physicians consider bronzing of the skin a symptom of only minor importance, while, on the other hand, others hold it to be the most important symptom of the disease. In his experimental

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<sup>10</sup> Kaufmann, E. Pathology, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929.

animals, Haitman noted a discoloration of body fat but said little about the occurrence of pigmentation

Fever was present during the exacerbations of the insufficiency. During the acute phases each of the patients manifested an increase in body temperature, in one instance to as high as 107 F. The body temperature during the quiescent interval, on the other hand, remained subnormal.

Pain in the abdomen is one of the most interesting symptoms of both the cases described here and those reported in the literature. When it occurs at the time of the most marked insufficiency, usually it is located in the upper part of the abdomen on either side and is associated with tenderness on deep pressure. Even when it occurs at an early stage in the development of the disease (as in the second case), the pain possesses the same characteristics. Neither Brenner nor Wells discussed this symptom, which, however, is noted in their protocols as having occurred. Rowntree and Snell stated that abdominal pain occurs in about half of the cases of Addison's disease. In Saphir and Binswanger's<sup>11</sup> patient with adlenal insufficiency the pain began on the right side of the abdomen and after twenty-four hours radiated all over the abdomen. Because of this appendectomy was performed, and while neither the appendix nor the adrenal glands showed evidence of acute inflammation, it is possible that the pain could have had a source other than an inflammatory process.

Symptoms in the central nervous system are very variable in their occurrence. When attacks of syncope, convulsions and shocklike crises occur, they are believed by Rowntree and Snell, for instance, to be on the basis of cerebral anemia incident to a marked decrease in the volume of blood. However, in our first case, just as in Rabinovitch and Barden's,<sup>12</sup> the spastic contraction of the right arm, which relaxed as the patient went into coma, is believed to have resulted from the hypoglycemia. Corresponding to this is the satisfactory immediate response to dextrose. Tedstrom,<sup>13</sup> following an analysis of a series of cases in which hypoglycemia resulted from hyperinsulinism, found that a large number of neurologic symptoms, such as occurred in our cases, are frequent in appearance.

On physical examination the patients, in general, are rather well developed and well nourished, in contrast to the obvious abnormal condition which one would expect to accompany congenital aplasia of either

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11 Saphir, O, and Binswanger, H. F. Suprarenal Cortical Insufficiency and Cytotoxic Contraction of the Suprarenals. *J. A. M. A.* **95** 1007 (Oct. 4) 1930.

12 Rabinovitch, J, and Barden, F. W. Hypoglycemia Associated with a Tumor of the Islands of Langerhans and with Adrenal Insufficiency, Respectively, *Am. J. M. Sc.* **184** 494, 1932.

13 Tedstrom, M. K. Hypoglycemia and Hyperinsulinism, *Ann. Int. Med.* **7** 1013, 1934.

the adrenal or other glands of internal secretion. Pigmentation usually is absent, but there may be a yellowish tint to the skin, with some deepening in shade of the normally pigmented areas. Hypotension is constant. At the periods when the adrenal insufficiency is most marked, the blood pressure falls to very low levels. The pupils may be large or of normal size, but usually they react normally. The optic disk may present inconstant findings suggestive of early choking, or there may be areas of pallor. The thyroid gland usually is normal but may be small. If râles occur, they are of incidental significance only. Abdominal tenderness, more or less widespread over the epigastrium, may be elicited at the time of the abdominal pain. The urinary tract is essentially normal on examination. The testicles may be small.

*Pathogenesis of the Symptoms*—Certain facts obtained by experimental work, while variously interpreted in regard to the normal physiology of the adrenal cortex, serve to explain the mode of production of the symptoms which occurred in our cases. Experimentally, it is found that whether the blood sugar is below or at the usual level, there is practically no response on its part to stimuli which ordinarily evoke hyperglycemia, nor is there storage of glycogen after administration of dextrose in adrenalectomized cats. The shift in water balance (which is simultaneous with the carbohydrate disturbance), such that the liver and muscles show an increase and the blood a decrease in hydration, is readily restored to normal by treatment and is subsequently easily maintained at that level. The fact that the latter response is so prompt, effective and continuous, whereas there is no change in the carbohydrate, even with continuous administration of saline solution, makes the disturbance of the carbohydrate phase the significant one. Clinically this interpretation holds as regards our cases, in that in both of them the onset and relief of the hypoglycemia determined the degree of the patient's prostration or relative well-being. However, there are undoubtedly additional disturbances, evident particularly by the pigmentation and the nonrelief by administration of carbohydrates in the terminal stages, of a more delicate nature, the mode of action of which is as yet undecided.

*Differential Diagnosis*—All the less obvious clinical entities, both common and rare, probably have been confused from time to time with the various epochs in and the manifestations of adrenal insufficiency.

In the presence of a fair degree of development and nourishment, the patients early in the course of the disease are most likely to be eliminated from deserved study by the diagnosis of the condition as psychoneurosis. True, it is only during a period of exacerbation that a definite diagnosis can be made, but this can be accomplished, with its resultant great satisfaction, if the patient receives a thorough initial examination and adequate subsequent ones. Classifications related to neurasthenia likewise decrease the possibility of early diagnosis.

Acute appendicitis suggested by the abdominal pain, is differentiated by a higher leukocyte count, which increases rather rapidly, localization of the pain, which might at first have been in the upper part of the abdomen to the region of McBurney's point and the absence of neurologic symptoms. Chronic appendicitis as a diagnosis is not acceptable, in the sense of recurring acute attacks, the criteria for differentiation are identical with those mentioned under a discussion of the individual attacks.

Certain other diagnostic terms which in themselves are open to controversy as indicating conditions in which neither the etiologic agent nor the underlying pathologic process is known, have been used to catalog the disorder from which the patient suffered early in the development of the disease. In this category are included gastric influenza and cyclic vomiting. Fortunately such diagnoses, even though incorrect, do represent a step toward the recognition of organic disease while at the same time they save the patient from operative procedures.

Epidemic encephalitis, probably because of its protean manifestations is the diagnosis not infrequently made during the early stages of the disease. The manifestations which are responsible for this probably are traceable in their entirety to the hypoglycemia which is present. In the face of symptoms of the central nervous system, which include not only those noted by Tedstrom but such bizarre ones as hemiplegia which disappears promptly with the administration of dextrose (Wechsler<sup>14</sup>) there is a strong possibility that adrenal insufficiency is the basis for the disturbance.

#### SUMMARY

The clinical aspects, including both symptomatology and diagnosis of early adrenal insufficiency resulting from partial or total atrophy of the adrenal glands, are discussed in this paper. The features stressed are the existence of a definite but hitherto considered vague group of symptoms, from the time of onset to the termination of the destructive process in the adrenals, the manifestation of exacerbations in the adrenal insufficiency by nausea, vomiting, hypotension, hypoglycemia, drowsiness even to coma and atypical neurologic signs, the occurrence of exacerbations during periods of physical, emotional or endocrine stress, the frequent absence of pigmentation, and the relief of symptoms during the periods of exacerbation in all but the terminal stages by the administration of dextrose.

Dr Henry A. Christian granted me permission to use material from the clinical records and Dr S. B. Wolbach the autopsy material from the cases reported.

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<sup>14</sup> Wechsler, I. S., discussion on Rinearson, E. H. and Moersch, F. P. Neurologic Manifestations of Hyperinsulinism and Other Hypoglycemic States. *J. A. M. A.* **103** 1198 (Oct 20) 1934.

# RELATION OF DISEASE OF THE LIVER TO ANEMIA

TYPE OF ANEMIA, RESPONSE TO TREATMENT, AND RELATION OF  
TYPE OF ANEMIA TO HISTOPATHOLOGIC CHANGES  
IN LIVER, SPLEEN AND BONE MARROW

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Attention has been directed recently in Germany,<sup>1</sup> Italy<sup>2</sup> and Austria,<sup>3</sup> as well as in this country,<sup>4</sup> to the occurrence of macrocytic anemia in association with disorders of the liver. The recognition of a hematologic picture in cases of disease of the liver resembling in many respects that of pernicious anemia is not new, as a review of the literature in an earlier communication<sup>4a</sup> indicated. Nevertheless, little significance was attributed to the association, and it has been only with the recently renewed interest in hematology that several investigators, working independently, have rediscovered this type of anemia.

In several respects the various observations are essentially in agreement. The anemia associated with disorders of the liver is rarely severe.<sup>5</sup> The macrocytosis affects the great majority of the red corpuscles,<sup>6</sup> which show relatively little variation in shape or size.<sup>7</sup> The lack of variation in the size of the corpuscles, however, does not distinguish

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From the Department of Medicine and the Medical Clinic, the Johns Hopkins University and Hospital

1 Schulten, H, and Malamos, B. Ueber Veränderungen der roten Blutkörperchen bei Lebererkrankungen, *Klin Wchnschr* **11** 1338 (Aug 6) 1932

2 Gamna, Carlo. Ueber Veränderungen der roten Blutkörperchen bei Lebererkrankungen, *Klin Wchnschr* **12** 348 (March 4) 1933

3 Fellinger, K, and Klima, R. Untersuchungen über Anämien bei Leberzirrhosen, *Wien klin Wchnschr* **46** 1191 (Oct 6) 1933

4 (a) Wintrobe, M M, and Shumacker, H B. The Occurrence of Macrocytic Anemia in Association with Disorder of the Liver, *Bull Johns Hopkins Hosp* **52** 387 (June) 1933. (b) Cheney, G. The Morphology of the Erythrocytes in Cirrhosis and Other Disorders of the Liver, *California & West Med* **39** 90 (Aug) 1933. (c) Van Duyn, John, Jr. Macrocytic Anemia in Disease of the Liver, *Arch Int Med* **52** 839 (Dec) 1933. (d) Goldhamer, S M. Liver Extract Therapy in Cirrhosis of the Liver, *ibid* **53** 54 (Jan) 1934

5 Schulten and Malamos<sup>1</sup> Gamna<sup>2</sup> Fellinger and Klima<sup>3</sup> Wintrobe and Shumacker<sup>4a</sup> Cheney<sup>4b</sup>

6 Schulten and Malamos<sup>1</sup> Gamna<sup>2</sup> Wintrobe and Shumacker<sup>4a</sup> Cheney<sup>4b</sup>

7 Fellinger and Klima<sup>3</sup> Wintrobe and Shumacker<sup>4a</sup> Cheney<sup>4b</sup>

the condition from pernicious anemia, for the distribution curves of the diameters of the red corpuscles are like those in cases of pernicious anemia with similar grades of anemia <sup>1a</sup> Nucleated red corpuscles are uncommon,<sup>1b</sup> and the fragility of the erythrocytes is normal.<sup>3</sup> Spontaneous remissions and relapses of the anemia may occur.<sup>8</sup> On clinical as well as postmortem evidence it was stated, or at least implied, by all the authors cited that the cases which they reported do not represent the accidental association of pernicious anemia with disease of the liver. It has also been pointed out that there is no relationship between the concentration of the bilirubin in the serum and the size of the red corpuscles.<sup>9</sup>

There is, however, a wide divergence of opinion as to the frequency of this type of anemia, and its cause is a subject of speculation. Schulten and Malamos<sup>1</sup> referred to the occurrence of macrocytosis in all cases of catarrhal icterus and cirrhosis of the liver, whereas Fellingner and Klima<sup>3</sup> found macrocytic anemia in eighteen of forty-eight cases (37 per cent) of cirrhosis, and Van Duyn<sup>1c</sup> found it in only five of twenty-eight cases (18 per cent) of the latter disease. No adequate study of the nature and severity of the anemia in relation to the changes observed microscopically in the liver and in the hematopoietic organs has been reported.

In the following pages is an account of the study of one hundred and thirty-two patients who suffered from various types of hepatic disorder. In all of the cases the mean volume and hemoglobin content of the red corpuscles were measured<sup>10</sup> and in the majority smears of blood were studied and other morphologic examinations were made. The observations usually were repeated at intervals. In some cases the effect on the blood of various types of treatment was studied. Gastric analysis and the van den Bergh test were carried out in a great number of cases, determinations of the icterus index and examinations of the urine for urobilinogen, urobilin and bile were made in every case. Through the courtesy of Dr. L. J. Soffer I am able to refer to the results of tests of hepatic function (bilirubin, bromsulphalein, galactose and levulose) which were carried out by him in fifty-one of the cases. Autopsy was performed in thirty-four cases.

#### TYPE OF ANEMIA

The observations on anemia are summarized in tables 1, 2 and 3. The cases of hepatic disease were divided into three large groups—those of cirrhosis, malignant disease, and miscellaneous disorders—and

<sup>8</sup> Fellingner and Klima.<sup>3</sup> Wintrobe and Shumacker.<sup>1a</sup>

<sup>9</sup> Schulten and Malamos.<sup>1</sup> Wintrobe and Shumacker.<sup>1a</sup> Cheney.<sup>1b</sup>

<sup>10</sup> Wintrobe, M. M. Macroscopic Examination of the Blood, *Am. J. M. Sc.*

each of the groups was further subdivided. In addition to the thirty-four instances in which autopsy was performed, there were thirteen cases in which the diagnosis was corroborated or corrected by exploratory laparotomy. The diagnosis in each of the remaining cases was based on the observations of several physicians.

The anemia in each case was classified on the basis of the mean volume and hemoglobin content of the red corpuscles, according to criteria outlined elsewhere<sup>11</sup>

In thirty cases (22.7 per cent) there was no anemia. Macrocytic anemia was present in forty-three cases, or 32.6 per cent, normocytic anemia, in forty, or 30.3 per cent, simple microcytic anemia, in three, or 2.3 per cent, and hypochromic microcytic anemia, in sixteen or 12.1 per cent.

TABLE 1—Type of Anemia in Cases of Cirrhosis of the Liver

Type of Cirrhosis	Number of Cases	No Anemia	Anemia			
			Macrocytic	Normocytic	Simple Microcytic	Hypochromic Microcytic
Nodular (Laennec)	23	0	6 + 2 (?)*	11	0	4
Biliary	5	1	3	1	0	0
Toxic	2	0	2	0	0	0
Pigment	2	1	1	0	0	0
Syphilitic	6	3	1 (?)	2	0	0
Unclassified	6	2	3	1	0	0
Total	44	7 (15.9%)	18 (3?) (40.9%)	15 (34.1%)	0	4 (9.1%)

\* In tables 1, 2 and 3, the cases of anemia which cannot with perfect certainty be classed as macrocytic, either because opportunity did not permit more than one examination of the blood to be made or because the mean corpuscular volume was only slightly greater than normal (95 or 96 cubic microns), are indicated by question marks.

The last-named type of anemia could be attributed in most instances to chronic loss of blood. Thus among the cases of cirrhosis (table 1), hypochromic microcytic anemia was noted only in association with the nodular (Laennec) type, in which obstruction of the portal blood vessels was associated with hemorrhage. Among the cases of malignant disease of the liver, hypochromic microcytic anemia was associated in three instances with carcinoma of the stomach and in these cases blood was found in the stools. In a case of carcinoma of the gall-bladder, ulcerations were found in the stomach and duodenum. Blood was found in the stools of one of the patients with carcinoma of the pancreas. In two of the cases recorded in table 3 in which hypochromic microcytic anemia was noted, there was a history of uterine bleeding.

11 Wintrobe, M. M. Anemia. Classification and Treatment on the Basis of Differences in the Average Volume and Hemoglobin Content of the Red Corpuscles, *Arch. Int. Med.* 54:256 (Aug.) 1934.



over a long period. Thus in all but five patients this type of anemia could be definitely attributed to the loss of blood.

In the three cases of simple microcytic anemia, the anemia was only moderate in degree, the red blood cell count averaging 3,850,000. The mean corpuscular volume was 78 cubic microns, and the mean corpuscular hemoglobin concentration, 33 per cent. One of the patients had congenital hemolytic jaundice, while in the other two there were complicating inflammatory processes.

In the cases studied, then, when anemia was noted, unless chronic loss of blood had occurred, the anemia was usually either of the normocytic or of the macrocytic type. The mean erythrocyte count in the cases in which normocytic anemia was present was 3,920,000,

TABLE 2—Type of Anemia in Cases of Malignant Disease of the Liver

Diagnosis	Number of Cases	No Anemia	Anemia			
			Macrocytic	Normocytic	Simple Microcytic	Hypo-chromic Microcytic
Primary carcinoma	4	2	2	0	0	0
Malignant disease secondary to carcinoma of stomach	10	1	2 ( )	5	0	3
Malignant disease secondary to carcinoma of gallbladder	2	0	1 ( )	1	0	1
Malignant disease secondary to carcinoma of pancreas	14	1	2	7	0	3
Malignant disease secondary to carcinoma of miscellaneous origin	5	0	1	4	1	0
Total	36	4	8 ( )	16	1	7
		(11.1%)	(22.2%)	(44.4%)	(2.8%)	(19.4%)
Malignant disease of liver associated with cirrhosis (included above)	8	1	5	1	0	1
		(12.5%)	(62.5%)	(12.5%)	0	(12.5%)

and the mean corpuscular volume was 87 cubic microns. The mean red cell count in the group of cases of macrocytic anemia was 3,480,000, and the mean corpuscular volume, 103 cubic microns.

According to the data recorded in the tables macrocytic anemia was somewhat more common than the normocytic type. Among the cases of macrocytic anemia were included, however, five instances of hemolytic anemia of obscure origin in which there were hepatomegaly and jaundice. In these five cases the morphologic findings in the blood were, without doubt, profoundly influenced by the destruction of the blood, and the anemia cannot be considered as fundamentally due to disease of the liver. The cases, therefore, may be excluded from the series. Among the thirty-eight instances of macrocytic anemia which remain, there are thirteen which cannot with certainty be grouped with those due to disease of the liver, either because opportunity did not permit more than one examination of the blood to be made or because

the mean corpuscular volume was only slightly greater (95 or 96 cubic microns) than normal<sup>11</sup> There remain twenty-five cases (21.9 per cent) in which, without any doubt, macrocytic anemia was associated with disease of the liver The mean red cell count in the twenty-five cases was 3,470,000 and the mean corpuscular volume, 104 cubic microns

#### DESCRIPTION OF ANEMIA AND RESPONSE TO TREATMENT

The macrocytic anemia observed in association with disorder of the liver has already been described<sup>4a</sup> As in pernicious anemia, the macrocytosis is, on the whole, inversely proportional to the degree of anemia The coefficient of correlation for 163 determinations in thirty-one cases of hepatic disease with macrocytic anemia is  $-0.5620 \pm 0.0361$

TABLE 3—*Type of Anemia in Cases of Miscellaneous Disorders of the Liver*

Diagnosis	Number of Cases	No Anemia	Anemia			
			Macrocytic	Normocytic	Simple Microcytic	Hypochromic Microcytic
Catarrhal jaundice	8	3	1 + 2 (?)	2	0	0
Jaundice due to arsphenamine	11	2	3 + 2 (?)	3	0	1
Acute yellow atrophy	6	5	0	1	0	0
Obstruction of bile duct	3	0	2 (?)	1	0	0
Amyloid disease	4	0	1 + 1 (?)	0	0	2
Chronic passive congestion	7	5	0	1	0	1
Miscellaneous hemolytic anemia with hepatomegaly	7	1	5	0	1	0
Other conditions	6	3	0	1	1	1
Total	52	19 (36.5%)	17 (7?) (32.7%)	9 (17.3%)	2 (3.9%)	5 (9.6%)

The coefficient of regression is mean corpuscular volume equals  $120.8 - 6 \times \text{red cell count (in millions)}$  These values are similar to those found in cases of pernicious anemia<sup>11</sup>

Morphologic evidence of increased hematopoiesis was rarely noteworthy in any of the cases Except in the cases of hemolytic anemia (table 3), nucleated red corpuscles were never found in the circulating blood, and even polychromatophilia was uncommon

It has been pointed out that rapid spontaneous remissions in the blood count occur not infrequently in cases of hepatic disease with anemia<sup>4a</sup> The observations reported here indicate that remissions, in which the erythrocyte count rises and the mean corpuscular volume changes toward the normal, are much more common in cases of hepatic disease with macrocytic anemia than in those with other types of anemia, such remissions having occurred in eighteen of twenty-five cases (72 per cent) of macrocytic anemia as compared with five of twenty cases (25 per cent) of the nonmacrocytic group It should be noted that

these changes in the blood took place even though, in some instances, the rise in the erythrocyte count was contrary to the general course of the patient's illness

Only in the cases of hypochromic microcytic anemia and of macrocytic anemia was treatment ever effective in increasing the blood count. In three cases of hypochromic microcytic anemia, one of which was associated with cirrhosis and two with malignant disease of the liver, iron therapy was definitely effective.

In four cases of macrocytic anemia, three of which were associated with cirrhosis and one with primary liver cell carcinoma, the intramuscular injection of liver extract was followed by a definite increase in the percentage of reticulocytes, a rise in the red cell count and a decrease in the mean corpuscular volume, such as occurs in pernicious anemia,<sup>12</sup> the reticulocyte response in patient E K R (table 4) was associated with a temporary increase in mean corpuscular volume (fig 1). In one patient who was given liver extract<sup>13</sup> orally and in three other patients with macrocytic anemia who were treated with liver extract administered intramuscularly, an increase in the number of erythrocytes and a decrease in mean corpuscular volume could less definitely be attributed to the therapy. A clearcut demonstration of the effectiveness of treatment could not have been expected in these cases, however, for the anemia was only moderate, the mean erythrocyte count being 3,960,000 as compared with an average count of 2,910,000 in the four cases in which treatment was definitely effective. In only one case of cirrhosis with macrocytic anemia was intramuscular liver therapy not followed by a decrease in the degree of anemia. The erythrocyte count in this case was 3,790,000, and the mean corpuscular volume, 97 cubic microns.

Since it has been shown that preparations of autolyzed yeast incubated with normal gastric juice are effective in causing a reticulocyte response in patients with pernicious anemia,<sup>14</sup> treatment with preparations of yeast was attempted in two cases of cirrhosis with macrocytic anemia and in one case of primary malignant disease of the liver with macrocytic anemia.

In one patient, whose gastric juice had already been shown to contain the "intrinsic factor,"<sup>15</sup> the administration of a preparation of

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12 Wintrobe, M. M. Relation of Variations in Mean Corpuscular Volume to Number of Reticulocytes in Pernicious Anemia. The Significance of Increased Bone Marrow Activity in Determining the Mean Size of Red Corpuscles, *J Clin Investigation* **13** 669 (July) 1934.

13 Liver Extract-Lilly, N. N. R., was used.

14 Strauss, M. B., and Castle, W. B. Nature of Extrinsic Factor of Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias, *New England J Med* **207** 55 (July 7) 1932.

TABLE 4—Observations at Autopsy in Thirty-Four Cases of Hepatic Disease

Patient	Diagnosis	Extent of Hepatic Damage, as Judged by†		Hematopoietic System*												
				Tests of Hepatic Function	Autopsy	Achlorhydria	Type of Anemia	R B C	C V	O C	Smear I E	Spont Rem	Resp to T	Bone Marrow		Spleen H F
														Hyperplasia	Met	
A E	Cirrhosis, biliary	+++	++		None	4 66	87	34	0			+	0	++		
L B	Cirrhosis, syphilitic	+++	+++		None	4 97	83	31	0			0	0	0		
E Se	Malignant disease, primary	+++	+++		None	5 95	85	30	0	+		++	0	+++		
M S	Malignant disease, primary	+++	+++		None	4 30	88	32		0		0	0	++		
W B	Malignant disease, secondary to that of pancreas	+++	+++	+	None	5 06	99	32	+	0		+	+	+++		
C G	Malignant disease, secondary to that of stomach, and early nodular cirrhosis															
R F	Acute yellow atrophy	+++	++	+	None	5 24	86	31				+	0	0		
Q S	Acute yellow atrophy	+++	+++	0	None	4 77	80	35				+	0	0		
W L	Acute yellow atrophy	+++	+++		None	4 50	93	28				+	0	0		
V B	Acute yellow atrophy	+++	+++		None	6 07	86	31	0			0	0	0		
J Bo R	Cirrhosis, biliary	+++	+++	0	None	5 48	81	30	0			++	0	+		
F K R	Cirrhosis, biliary (Hanot)	+++	+++	0	Macrocytic	2 50	103		++		++	++	0	++		
A Z	Cirrhosis, toxic	+++	+++	0	Macrocytic	2 66	117		++		++	++	0	++		
L S	Cirrhosis, toxic	+++	+++	0	Macrocytic	3 64	102		++		++	++	0	++		
R P	Cirrhosis, pigment	0	++	0	Macrocytic	3 11	106		++		++	++	0	++		
F H	Malignant disease, primary, and biliary cirrhosis	++	+++	0	Macrocytic	3 21	97		0	+	++	++	0	+		
I C	Malignant disease, secondary to that of ascending colon, and slight biliary cirrhosis	++	+++	0	Macrocytic	3 15	101		++		++	++	0	+++		
M M	Malignant disease, secondary to that of gallbladder, and biliary cirrhosis		+++	0	Macrocytic	2 60	100					++	0	+++		
M C	Malignant disease, secondary to that of pancreas, and biliary cirrhosis		+++	+	Macrocytic	3 25	96		++	++	++	++	0	++		
G B	Malignant disease, secondary to that of pancreas, and biliary cirrhosis		+++	+	Macrocytic	3 50	99				+	0?	0	+++		
C S	Amyloidosis		+++		Macrocytic	2 22	105		+			+	0	+		
P F B	Cirrhosis, nodular	+++	+++	+	Macrocytic	2 48	106		++	+		+	0	+		
S C	Cirrhosis, nodular	+++	+++		Normocytic	3 21	86		++			+	0	0		
A I	Malignant disease, secondary to that of stomach	+++	+++	0	Normocytic	3 04	80		0	0		0	0	0		
I L	Malignant disease, secondary to that of gall bladder	0	+	+	Normocytic	4 00	81				+	+	0	0		
I F	Malignant disease, secondary to that of gall bladder		+	+	Normocytic	4 18	84		+			+	0	0		
T H	Malignant disease, secondary to that of pancreas		+	0	Normocytic	3 94	86			0		0	0	0		
F So	Malignant disease, secondary to that of pancreas	0	+++	0	Normocytic	4 45	87		0			0	0	0		
I Bl	Malignant disease, secondary to that of pancreas, and early biliary cirrhosis		+++	0	Normocytic	4 41	80		0			+	+	+++		
A T	Malignant disease, secondary to that of lung	++	+++	0	Normocytic	2 71	91		0			0	0	0		
Q S	Acute yellow atrophy	+++	+++	+	Normocytic	3 72	87		0	0		0	0	0		
L S	Malignant disease, secondary to that of stomach		+++	+	Hypochromic microcytic	4 18	89					0	0	0		
G R	Malignant disease, secondary to that of stomach, and slight biliary cirrhosis	++	++	+	Hypochromic microcytic	2 65	65		0			0	0	0		
I G	Malignant disease, secondary to that of pancreas		++	+	Hypochromic microcytic	2 85	78		0		+	+	0	0		
			++	+	Hypochromic microcytic	3 39	77		0		++	+	0	0		

\* R B C indicates the number of red corpuscles in millions per cubic millimeter, C V, mean corpuscular volume in cubic microns, C C, corpuscular hemoglobin concentration in percentage, Smear I F, evidence of increased erythropoiesis as indicated by anisocytosis, polychromatophilia, reticulocytosis or the presence of nucleated red corpuscles, Spont Rem, spontaneous increase of erythrocyte count, Resp to T, response to treatment, Met, metastases in bone, Spleen H F, hemato poietic foci in spleen

† The extent of damage is indicated by symbols as follows: slight, +, moderate, ++, extensive, +++, very extensive, +++++

autolyzed yeast (Vegex), 1 ounce (28 Gm) daily for nine days, was associated with a rise in the reticulocyte count from 0.6 per cent to 1.8 per cent on the fifth day after commencement of the treatment and an increase in the erythrocyte count from 4,080,000 to 4,260,000. The administration to another patient of yeast tablets,<sup>14a</sup> 6 daily, and of a preparation of purified wheat embryo (Embo) rich in vitamins B<sub>1</sub> and E and containing large amounts of vitamin A and G, 2 ounces

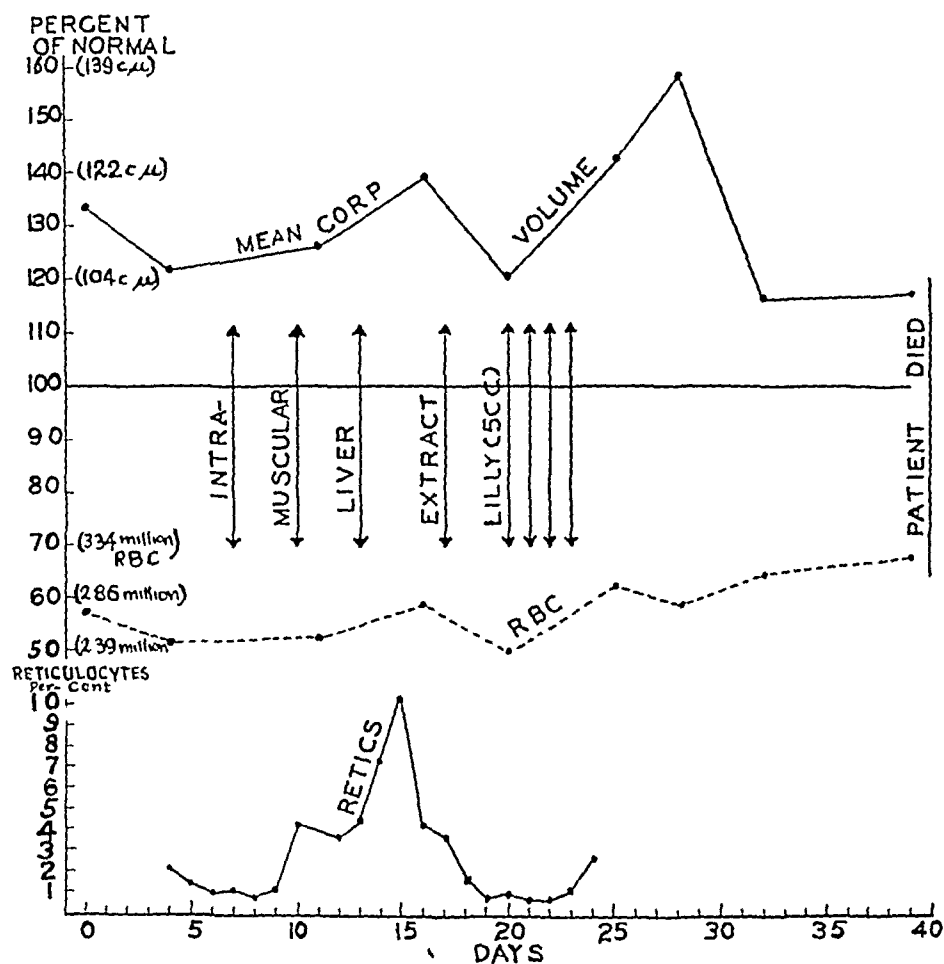


Fig 1—Effect of intramuscular injection of liver extract in a case of biliary cirrhosis with macrocytic anemia (E K R, table 4). The mean corpuscular volume and the number of red corpuscles are represented in proportion to the normal values, the ideal for both being 100 per cent. Reticulocyte counts were unfortunately not made after the twenty-fourth day, but the second temporary increase in mean corpuscular volume suggests that there was an added response to the last four intramuscular injections.

daily, was not followed by any changes in the blood. In the same patient, however, nine months later, when the anemia was more severe,

14a Each tablet is said to contain "200 mg of standardized vitamin fraction, according to Osborne and Wakeman" (J Biol Chem 40:383 [Dec] 1919).

the administration of a specially prepared concentrate of vitamin B complex,<sup>15</sup> 24 Gm daily for eleven days, was followed by a somewhat irregular increase in the number of reticulocytes, from 2 to 47 per cent, and an increase in the erythrocyte count from 3,410,000 to 3,920,000. The administration to a third patient of brewer's yeast, 9 tablets daily, was not followed by any changes in the percentage of reticulocytes or the erythrocyte count, but the latter was already 3,700,000 and had risen in response to intramuscular liver therapy.

Treatment with "secondary anemia" liver extract and iron was attempted in one case of cirrhosis with macrocytic anemia. An amount corresponding to 400 Gm of liver and 2.6 Gm of iron and ammonium citrate was given daily, but no change in the erythrocyte count (3,790,000) or in the percentage of reticulocytes followed. This is contrary to Cheney's experience,<sup>4b</sup>

TABLE 5—*Relation of Extramedullary Hematopoiesis (Spleen) to Type of Anemia*

Diagnosis	Number of Cases	No Anemia	Anemia			
			Macrocytic	Normocytic	Simple Microcytic	Hypo chromic Microcytic
Hepatic disease						
Cases with hematopoietic foci	11	3	7	1	0	0
Cases with no hematopoietic foci	15	7	0	7	0	1
Miscellaneous diseases						
Cases with hematopoietic foci	6	1	4	1	0	0
Cases with no hematopoietic foci	17	1	0	8	6	2

#### HISTOLOGY OF THE HEMATOPOIETIC ORGANS

Dr. Arnold Rich has called my attention to the occurrence of foci of extramedullary hematopoiesis in the spleens of some of the patients who died of hepatic disease. The following observations regarding the presence or absence of such foci were made by him without any knowledge of the type of anemia which had been present in the cases.

The foci observed were usually numerous and contained normoblasts, frequently macroblasts, and occasionally myeloid leukocytes, in groups of from 6 to 20 cells (fig. 2). Such nests of cells were found in the spleens of eleven patients and were absent in fifteen. The spleens of the eight remaining patients, data on whom are recorded in table 4, were unsatisfactory for examination because of autolysis.

In seven of the eleven cases of hepatic disease in which foci of extramedullary blood formation were observed at autopsy, the anemia had been of the macrocytic type (table 5). No anemia had been observed in three cases, but it is interesting to note that macrocytosis

15 This preparation was furnished by Mead Johnson and Company. It contained 600 Chick and Roscoe vitamin B complex units per ounce (28.35 Gm.)

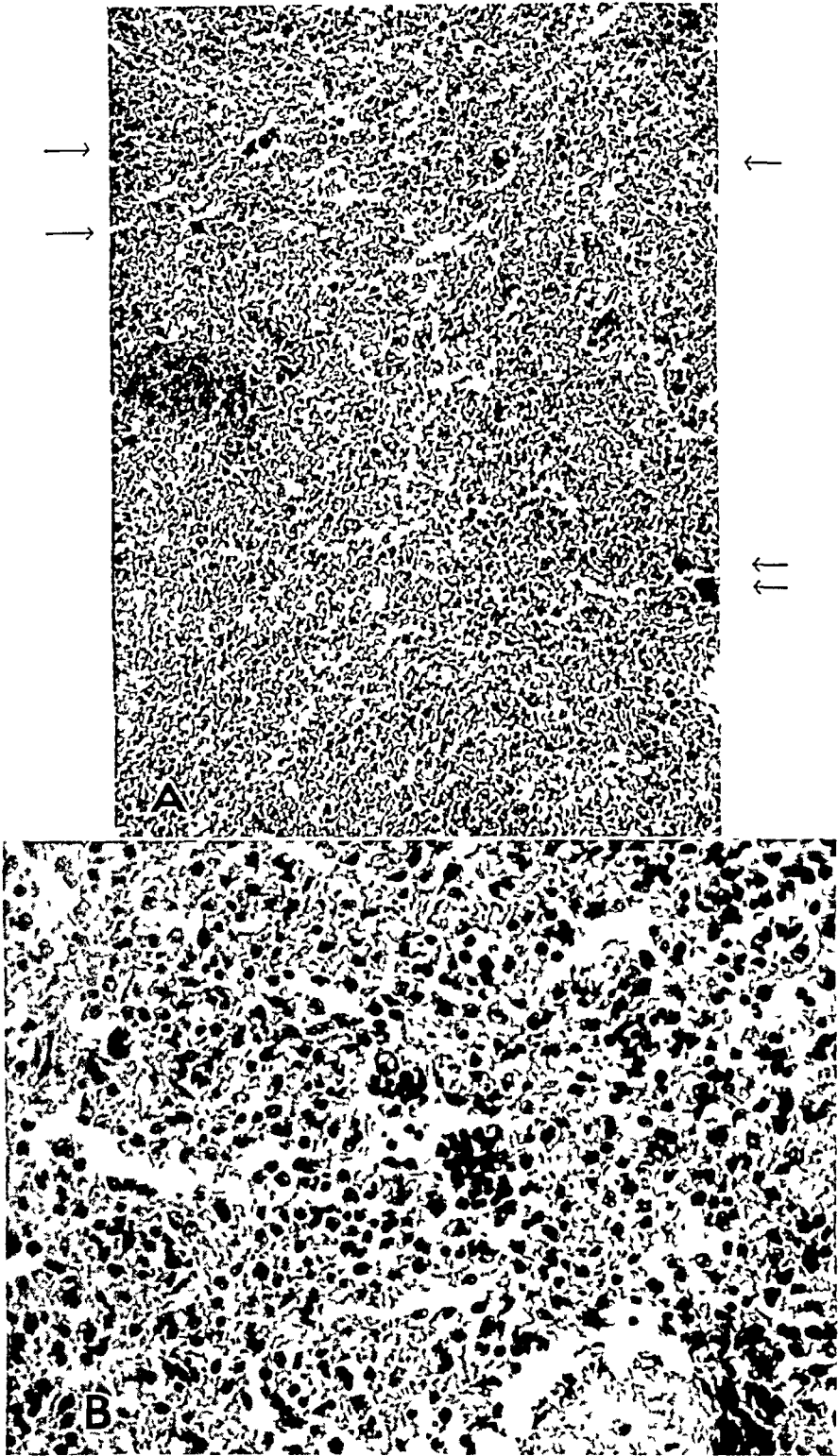


Fig 2—Foci of hematopoiesis in the spleen of a patient with metastatic carcinoma of the liver, biliary cirrhosis and macrocytic anemia (M C, table 4) In *A* (low power magnification,  $\times 100$ ) the foci appear as small groups of deeply staining cells In *B* one of the groups is shown in greater magnification ( $\times 400$ )

(mean corpuscular volume 99 cubic microns) had been repeatedly found in one of the nonanemic patients (W B, table 4). A metastatic nodule of tumor tissue was noted in a vertebra of one patient (E So, table 4) in whom the anemia had been normocytic.

The high incidence of macrocytic anemia among the cases of hepatic disease in which extramedullary foci of blood formation were noted is in striking contrast to the complete absence of this type of anemia among the cases in which such foci were not observed (table 5).

For purposes of comparison, the spleens of twenty-three patients who had died of disease other than that of the liver in whose cases data concerning the type of anemia were available were examined. The diseases included pneumonia (three cases), nephritis (two), pellagra (two), hypophyseal cachexia and sepsis (one), aplastic anemia (three), benzene poisoning (one), sickle cell anemia (two), multiple myeloma (one), erythremia (one), pernicious anemia (three), multiple thromboses of the spleen (one), granulocytopenia (one), Hodgkin's disease (one) and carcinoma of the cervix (one). Examples of acute tumor of the spleen and of leukemia were excluded.

Foci of blood formation were observed in the spleens of six patients, one of whom had died of erythremia, one of Hodgkin's disease with widespread involvement of the bone marrow, three of pernicious anemia and one of multiple thromboses of the spleen. In the first there was no anemia, in the second there was normocytic anemia and in the other four the anemia had been macrocytic (table 5). In none of the remaining seventeen cases was extramedullary blood formation observed, nor had macrocytic anemia been found.

In all cases, then, both those of hepatic disease and the control group in which macrocytic anemia had been observed in association with other diseases, foci of hematopoiesis were noted in the spleen. In only two instances were the foci associated with any other type of anemia, but in four cases in which they were observed there had been no anemia.

In none of the cases were foci of blood formation observed in the liver.

An attempt has been made in table 4 to indicate the extent of blood formation in the bone marrow in the cases in which autopsy was performed. The estimate is based on the study of the femoral and vertebral bone marrow.

In all the cases of macrocytic anemia there was some evidence of increased blood formation in the femoral bone marrow. In five instances there was definite hyperplasia. On the other hand, although there was some indication of increased hematopoiesis in a few of the



cases of nonmacrocytic anemia, it was of no greater degree than in cases in which there was no anemia and was distinctly less than in the group of cases of macrocytic anemia. It is noteworthy that the cases of macrocytic anemia were, on the whole, little more severe than those of nonmacrocytic anemia.

#### RELATION OF MACROCYTIC ANEMIA TO TYPE OF HEPATIC DISEASE

A comparison of the data presented in tables 1, 2 and 3 indicates that macrocytic anemia was most commonly associated with cirrhosis of the liver. The relatively high incidence of macrocytic anemia in cases of cirrhosis becomes even more striking when the cases of hemolytic anemia and the cases in which the diagnosis of macrocytic anemia was doubtful are excluded, for then the incidence of macrocytic anemia in cases of cirrhosis becomes 36.6 per cent (15 cases), as compared with 16.1 per cent (five) in cases of malignant disease and 12.5 per cent (five) in cases of miscellaneous disorders of the liver. It is significant to note, moreover, that in all of the five cases of malignant disease of the liver in which macrocytic anemia occurred, cirrhosis of various degrees was associated with the malignant process. On the other hand, no instance of macrocytic anemia occurred among ten cases of malignant disease of the liver uncomplicated by cirrhosis.

#### RELATION OF EXTENT OF HEPATIC DAMAGE TO TYPE OF ANEMIA

The macroscopic and microscopic examinations of the liver in the cases in which autopsy was performed give the distinct impression that macrocytic anemia occurred in those cases in which damage to the liver was particularly great and extensively distributed. Such comments as the following by independent observers are typical: "Advanced cirrhosis. The whole process of scarring is finely and evenly distributed" (patient A. Z.), "the intervening liver tissue was seldom of wide enough extent to permit gaining an idea of the condition of the liver itself" (patient J. H.), "most extreme biliary cirrhosis" (patient G. B.), "the cirrhosis is diffuse and finely distributed so that individual cells are separated from one another by connective tissue" (patient E. K. R.). Furthermore there was in these cases little or no regeneration of liver tissue.

In the cases of malignant disease in which macrocytic anemia was present, the regularity with which cirrhosis was associated with the malignant process further supports the impression that macrocytic anemia occurred in cases in which there was great damage to the liver. In the cases of malignant disease the total extent of destruction of the liver tissue was great indeed. On the other hand, in each of the three cases in which malignant disease was combined with cirrhosis (C. G.,

J B1, G R) and in which macrocytic anemia had *not* been noted, the cirrhosis was described as "early" or "slight" and the metastatic involvement was of only slight or moderate extent

In table 4 an attempt has been made to indicate the extent of damage to the liver in each case, as judged by the postmortem examination and, in a few instances, as indicated by tests of hepatic function. Although the estimate of the extent of damage to the liver is admittedly only approximate, it serves to contrast the degree of damage in the cases of macrocytic and those of nonmacrocytic anemia. Of the eleven cases of macrocytic anemia, in seven the damage to the liver is designated according to postmortem observations as very extensive (++++), and in four, as moderately extensive (+++) Of the cases of nonmacrocytic anemia, in seven the damage is designated as very extensive, in two, as moderately extensive, in ten, as moderate (++), and in four, as slight (+)

It is also apparent from the study of these cases that if extensive damage to the liver leads to the development of macrocytic anemia, it is hepatic disease of long standing which is important. Of the five cases of acute yellow atrophy, although damage to the liver was extreme, no anemia was observed in four, and only slight, normocytic anemia was present in the fifth. It may be added that if the cases of acute hepatic disease are omitted, the number of cases of nonmacrocytic anemia with very extensive damage to the liver is reduced to two. It is interesting to note that in neither of these two cases had any anemia been observed but in one, macrocytosis was nevertheless repeatedly found.

#### COMMENT

The observations recorded indicate that in cases of hepatic disease, except when loss of blood or a complicating infection is present, anemia, when it develops, is either of the normocytic or of the macrocytic type. The macrocytic anemia observed is, in many respects, like pernicious anemia, although it is rarely as marked as the latter, it is morphologically similar, if not identical. Spontaneous remissions in the anemia may occur. Intramuscular liver therapy was followed in several cases by definite reticulocytosis and a decrease of anemia, such as occurs in cases of pernicious anemia.

In none of the cases was any clinical or postmortem evidence obtained which might have permitted the anemia to be attributed to any cause other than the hepatic disease or the associated malignant process. Achlorhydria was, in fact, less common (40 per cent) in cases in which macrocytic anemia was noted, than in the cases of nonmacrocytic anemia (64 per cent). Nor was any other cause of macrocytic anemia such as acute loss of blood, discovered.

It seems to be a justifiable assumption, then, that the hepatic disease is the cause of the macrocytic anemia. In this connection it is important to emphasize that in the cases of macrocytic anemia the hepatic disease was of such long duration and was so widespread through the organ that little functioning liver tissue remained. Macrocytic anemia appears to be especially common in cases of cirrhosis of the liver, and in this disease the illness is characteristically chronic and the lesions widespread. In an earlier communication<sup>1a</sup> it was suggested that macrocytic anemia develops in a patient with hepatic disease as the result of faulty storage of the hematopoietic principle. There has been ample confirmation<sup>16</sup> of the experimental results of Richter, Ivy and Kim,<sup>17</sup> which first demonstrated that this principle is stored in the liver. Of further significance is Goldhamer's report<sup>16b</sup> that the liver of a patient who died of cirrhosis and macrocytic anemia was ineffective in the treatment of a patient with pernicious anemia whereas the liver of a patient who died of acute yellow atrophy contained the active hematopoietic principle. The evidence available at present suggests, then, that when damage to the liver is so extensive that storage is interfered with and when it has been of sufficient duration to permit exhaustion of the hematopoietic principle already present, macrocytic anemia develops.

There is no evidence to indicate that in the cases of hepatic disease there is any difficulty in utilizing the extrinsic factor from the diet or that the liver has any other function concerning the hematopoietic principle except that of simple storage. We have been able to demonstrate the presence of the intrinsic factor in the gastric juice of one patient with macrocytic anemia associated with hepatic disease.<sup>1a</sup> Unfortunately, the experiments already described, in which the effect on the blood of the oral administration of the extrinsic factor was studied, are not conclusive, but they tend to support the belief that patients with disease of the liver and macrocytic anemia are able to utilize the extrinsic factor to form hematopoietic principle. The ability to utilize the extrinsic factor may explain why in cases of hepatic disease with macrocytic anemia the anemia is rarely severe, and the consumption of various amounts of active hematopoietic principle may explain the fluctuations in the degree of anemia which have been so frequently observed.

The foci of blood formation observed in the spleens of the patients who had hepatic disease with macrocytic anemia are of considerable

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16 (a) Wilkinson, J. F., and Klein, L. The Haemopoietic Activity of the Normal and Abnormal Human Liver, *Quart J Med* **3** 341 (July) 1934. (b) Goldhamer, S. M., Isaacs, R., and Sturgis, C. S. The Rôle of the Liver in Hematopoiesis, *Am J M Sc* **188** 193 (Aug) 1934.

17 Richter, O., Ivy, A. C., and Kim, M. S. Action of Human "Pernicious Anemia Liver Extract," *Proc Soc Exper Biol & Med* **29** 1093 (June) 1932.

interest because such foci have rarely been observed in adults except in cases of pernicious anemia, osteosclerosis and carcinomatous replacement of the bone marrow and in rare cases of sepsis. Meyer and Heineke<sup>18</sup> originally described small collections of normoblasts, myelocytes and lymphocyte-like cells in the spleens of seven patients who had pernicious anemia. They observed similar changes in the liver, but these were much less constant. Schridde<sup>19</sup> confirmed the findings. Myeloid metaplasia in the liver and spleen in cases of osteosclerosis and carcinomatosis of the bone marrow was first noted by Askanazy<sup>20</sup> and by Donhauser<sup>21</sup>. All of these observations have been confirmed,<sup>22</sup> and are generally quoted,<sup>23</sup> but there are few reports concerning the occurrence of extramedullary hematopoiesis in any other conditions in adults. Weil<sup>24</sup> described hematopoietic foci in the spleens of persons dying of various infectious diseases, especially variola, but in cases of the acute tumor of the spleen arising from infection myeloid metaplasia is extremely difficult to distinguish.<sup>22a</sup> Meyer and Heineke<sup>18</sup> found extramedullary blood formation in the spleen in two cases of secondary anemia of septic origin, and Schridde<sup>19</sup> also stated that it may occur, though rarely. Brannan<sup>25</sup> observed blood formation in the spleen, liver and broad ligaments of a woman who died of anemia and sepsis following incomplete abortion, and hematopoietic foci have even been observed developing in adipose tissue in cases of sepsis.<sup>26</sup> Meyer and Heineke<sup>18</sup> included among their patients showing extramedullary hematopoiesis one patient with "anemia with cardiac disease." Draper<sup>27</sup>

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18 Meyer, Erich, and Heineke, Albert. Ueber Blutbildung in Milz und Leber bei schweren Anämien, *Verhandl d deutsch path Gesellsch* **9** 224, 1905

19 Schridde, H. Ueber Regeneration des Blutes unter normalen und krankhaften Verhältnissen, *Centralbl f allg Path u path Anat* **14** 865, 1908

20 Askanazy, M. Ueber extrauterine Bildung von Blutzellen in der Leber, *Verhandl d deutsch path Gesellsch* **7** 58, 1904

21 Donhauser, J. L. The Human Spleen as an Haemoplastic Organ, as Exemplified in a Case of Splenomegaly with Sclerosis of the Bone-Marrow, *J Exper Med* **10** 559, 1908

22 (a) Rich, A. R. Personal communication to the author. (b) Jordan, H. E. Extramedullary Erythrocytopoiesis in Man, *Arch Path* **18** 1 (July) 1934

23 Naegeli, O. *Blutkrankheiten und Blutdiagnostik*, Berlin, Julius Springer, 1931, p 127. Boyd, William. *The Pathology of Internal Diseases*, Philadelphia, Lea & Febiger, 1931, p 564

24 Weil, E. *Le sang et les réactions défensives de l'hématopoïèse dans l'infection variolique*, Paris, G. Steinheil, 1901, quoted by Brannan<sup>25</sup>

25 Brannan, Dorsey. Extramedullary Hematopoiesis in Anemias, *Bull Johns Hopkins Hosp* **41**:104 (Aug) 1927

26 Petri, E. Ueber Blutzellherde im Fettgewebe des Erwachsenen und ihre Bedeutung für die Neubildung der weissen und roten Lymphknoten, *Virchows Arch f path Anat* **258** 37, 1925

27 Draper, George. Blood Formation in Liver and Spleen in Secondary Anaemias. Report of a Case, *Bull Ayer Clin Lab, Pennsylvania Hosp* **6** 14, 1910

observed many small nests of myelocytes throughout the spleen of a patient with severe anemia who died of chronic nephritis. Schridde<sup>19</sup> failed to observe extramedullary blood formation in cases of post-hemorrhagic anemia, either acute or chronic. It may be added that tumor-like growths of extramedullary hematopoietic tissue have been observed in several cases of hemolytic jaundice,<sup>28</sup> and actual heterotopia of the bone marrow<sup>25</sup> has been reported.

Among the cases of hepatic disease described here there were only two in which any of the conditions known to be associated with the development of extramedullary hematopoietic foci were discovered. In each of these cases one small vertebral metastasis was noted. A single metastasis can hardly be considered as an adequate stimulus for the development of extramedullary hematopoiesis, but it is possible that other bone metastases were present, which were not discovered. Be that as it may, there remain nine cases in which there was found no cause for the hematopoietic foci other than the hepatic disease. Certainly one could not attribute their formation to the development of severe anemia, for the anemia was little more severe in the cases in which hematopoietic foci were found than in those in which they were absent, the mean erythrocyte count for the former being 3,730,000 and for the latter 4,410,000.

Among the reports of cases of hepatic disease with macrocytic anemia which were reviewed in an earlier communication,<sup>11</sup> only in the case of pigmentary cirrhosis reported by Bittorf was there mention of the observation of hematopoietic foci in the spleen. The failure to discover such foci is, however, probably of little significance, for they can be readily overlooked, as they were in the routine study in the majority of the cases of hepatic disease described here. In addition to Bittorf's observation, already mentioned, only two reports of cases of hepatic disease have been found in which myeloid changes in the spleen had been observed. Gandy and Bornaï-Legueule<sup>29</sup> noted myeloid changes in the spleen of a patient with severe (possibly macrocytic) anemia who showed marked splenomegaly and pigmentation of the liver with beginning cirrhosis. Pissavy and Thibaut<sup>30</sup> described a patient with obstructive jaundice, hepatomegaly and splenomegaly and

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28 Dawson, B. E. Hume Lectures on Hemolytic Icterus, *Brit. M. J.* **1**: 963 (June 6) 1931. Hunter, Donald. Personal communication to the author. Hartfall S. J., and Stewart, M. J. Massive Paravertebral Heterotopia of Bone Marrow in a Case of Acholuric Jaundice, *J. Path. & Bact.* **37**: 455 (Nov.) 1933. Rich<sup>22a</sup>

29 Gandy, C., and Bornaï-Legueule. Anémie splénique hyperplasie myéloïde de la rate, hémosiderose viscérale, *Bull. et mem. Soc. méd. d'hôp. de Paris* **23**: 694, 1906.

30 Pissavy, A., and Thibaut. Anémie hépato-splénomégaly avec réaction hématopoïétique complexe, *Bull. et mem. Soc. méd. d'hôp. de Paris* **34**: 813, 1912.

pronounced (macrocytic?) anemia. The anemia had been aggravated, if not largely caused, by repeated epistaxes. The liver at autopsy showed slight cirrhosis, and the spleen contained hematopoietic foci. Weil and Clerc<sup>31</sup> noted myeloid changes in the spleen in a group of twelve cases in which the condition was characterized clinically by distinct splenomegaly and severe anemia with marked normoblastosis and leukocytosis. The liver was increased in size in eight instances, but this was never a prominent symptom, nor were there signs of hepatic dysfunction. The cases are, therefore, probably not analogous to those discussed in this paper.

The presence of foci of extramedullary hematopoiesis in cases of chronic and widespread hepatic disease with macrocytic anemia is another point of similarity to pernicious anemia, in which, it has been already pointed out, blood formation in the spleen is common. When the similarity is considered in the light of the observations already recorded, it is reasonable to suspect that the development of extramedullary blood formation may occur in both instances as the result of the same fundamental abnormality, namely, a deficiency in a necessary hematopoietic principle.

Another analogy presents itself, which is concerned with the biologic significance of macrocytosis in general. This analogy is afforded by observing the regularity with which macrocytosis and extramedullary blood formation were associated in the cases studied, both in the group of cases of disease of the liver and in the control group, and by recalling the fact that macrocytosis is a characteristic of the blood of the fetus<sup>32</sup> and new-born infant, just as extramedullary hematopoiesis is normal at that period of life. It will be interesting to determine whether macrocytosis and extramedullary blood formation are consistently associated and whether or not they represent, in disease, a return to the type of blood formation characteristic of the fetus and the lower vertebrates.

#### SUMMARY AND CONCLUSIONS

A study of the blood in one hundred and thirty two cases of hepatic disorder of various etiology is recorded. The postmortem observations in thirty-four of the cases are considered in relation to the type of anemia observed.

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31 Weil, P. E., and Clerc, A. De la splénomégalie chronique avec anémie et myélémie, *Arch. gén. de méd.* **8** 560, 1902.

32 Wintrobe, M. M., and Shumacker, H. B., Jr. Comparison of Hematopoiesis in the Fetus and During Recovery from Pernicious Anemia, *J. Clin. Investigation* **14**:837 (Nov.) 1935, Erythrocyte Studies in the Mammalian Fetus and Newborn, *Am. J. Anat.* **58** (March) 1936, to be published.

Except when hemorrhage or a complicating infection was associated with it, anemia associated with hepatic disease was either normocytic or macrocytic

The macrocytic anemia was morphologically similar to if not identical with that seen in pernicious anemia. Like the latter, it manifested spontaneous remissions and was influenced by intramuscular liver therapy

Macrocytic anemia was found in cases of hepatic disease of some duration and of wide extent. It was most common in cases of cirrhosis of the liver. It was not found in cases of acute necrosis of the liver or when the damage to the liver was only slight or moderate in severity

Foci of blood formation in the spleen were observed in the cases of hepatic disease with macrocytic anemia as well as in association with other forms of macrocytic anemia, but, with two exceptions, they were not noted in association with any other type of anemia

The observations recorded support the hypothesis that macrocytic anemia in cases of hepatic disease results from an inability to store a necessary hematopoietic principle

# NEURITIC MANIFESTATIONS IN DIABETES MELLITUS

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A man (case 9,009) of quiet and controlled temperament was brought in an ambulance to the hospital. He was moaning and writhing in pain, although his pupils were already contracted by morphine administered for an attack of suspected ureteral colic. A second patient (case 10,349), a former football player and coach, was admitted to the hospital because of such unaccountable depression, restlessness and severe burning sensations in his feet that he could not sleep. A third patient (case 10,405) was admitted because paralysis of the muscles of the foot had prevented his working for the preceding two months. A fourth patient (case 8,428), a man 30 years of age, was admitted to the hospital because of gangrene following a burn from an electric pad applied to a painful foot and lower part of the leg. All four suffered from diabetic neuritis. In 1864 Marchal de Calvi drew attention to the causal relationship between diabetes and disturbances of the nervous system, and in 1931 Wendt and Peck again emphasized diabetic neuritis. Sevringhaus (1931) reported diminished activity of the reflexes in 57.3 per cent of 75 diabetic patients studied for this condition, and Bolduan (1932) observed that 2 per cent of the population died of diabetes. Thus one sees that a large number of persons are afflicted with diabetic neuropathy.

## HISTORY OF THE CONDITION

*Early Observations* —In 1864, when Duménil was drawing attention to multiple neuritis and shortly after Bernard and his co-workers by their experiments had given such impetus to the consideration of lesions of the central nervous system as a cause of diabetes, Marchal de Calvi pointed out that diabetes may be the cause rather than the result of neurologic disturbances. Even prior to 1864, symptoms suggestive of diabetic neuropathy had been described.<sup>1</sup> As summed up by Auché (1890), the reports of the early writers,<sup>2</sup> from 1864 to 1884, dealt in a rather theoretical manner with the mechanism causing the nervous symptoms, which were described to a limited extent.

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From the George F. Baker Clinic, Elliott P. Joslin, M.D., Medical Director of the New England Deaconess Hospital, Boston.

1 Rollo (1797) Frank (1842) Bardsley (1807) Billiard (1852)

2 Christi-Buici (1873) Worms (1880) Mary (1881) Raymond and Oulmont (1881) Berger (1882) Drasche (1882) Rosenstein (1882) Charin and Guignard (1882) Bouchard (1882) Bernard and Féré (1882) Demange (1883) Barth (1883) Dreyfous (1883) Dieulafoy (1884) Cornillon (1884)



*Later Observations*—According to Charcot (1890), Bouchard presented in a lecture in 1881 his observation that the knee jerks are often absent in diabetic persons, he published this report in 1884. Marinian in the same year published a similar report, and, according to Woltman and Wilder (1929) and Wight (1931), Althaus also recognized this pseudotabes of diabetes in 1884. From then until 1910 the literature concerning diabetic neuropathy increased rapidly. Since 1910 sporadic descriptions have appeared, one of the most notable, other than those in such comprehensive books as Joslin's (1928) and von Noorden and Isaac's (1927), being that by Woltman and Wilder (1929). After Bouchard's paper appeared, reports of the signs, as well as of the symptoms, became more numerous. Pryce (1887) described a sluggish pupillary reaction and ataxia, the latter of which was also mentioned by Pavy (1887) and von Leyden (1888). Von Leyden, who in 1880 had stimulated interest in nonspecific multiple neuritis, in 1888 reported cases of diabetes with paralysis and separated diabetic neuritis into three groups: the hyperesthetic, the paralytic and the ataxic. Von Ziemssen (1885) attributed the neuralgia of diabetes to peripheral neuritis but gave no pathologic proof. Von Hosslin (1886) commented on the absence of paralysis in diabetic persons with neuralgia, but in 1890 typical cases of diabetes with paralysis were reported by Althaus, Auché, Buzzard and Charcot. The case reported by Althaus was one of mononeuritis of the circumflex nerve, with atrophy of the muscles. Trophic ulcers were present in a case reported by Pryce (1887) and in one recorded by Buzzard (1890), and Raven (1887) reported a case with associated atrophy of the optic disk. Auché (1890), in a good article, summed up the literature and stated that the nervous complications of diabetes may involve all nerve functions: motor, sensory, special sensory, intellectual and nutritional. He listed among the symptoms pain especially at night, deep pain, lancinating and lightning pain, paresthesia, hyperesthesia, anesthesia, tenderness of nerves, changes in the reflexes, paralysis and vasomotor and trophic difficulties. He did not think that there was involvement of the bladder and rectum. He believed that this form of neuritis was not rare in diabetes, and he compared it with alcoholic neuritis, which had been done by von Leyden (1888), Minor (1889), Charcot (1890) and Buzzard (1890). Thus one sees that by 1890 the clinical picture of diabetic neuritis was rather complete.

Since 1890, many phases of diabetic neuritis have been described. Williamson wrote several articles. Lepine (1909), Labbé (1922), von Noorden and Isaacs (1927) and Joslin (1928) devoted sections in their books to the subject. Woltman and Wilder (1929) wrote a comprehensive paper, especially on the pathologic process, and Root and Rogers (1930) reported 11 cases with associated paralysis.

## OBSERVATIONS

*Selection of Cases*—The cases described here were selected from those of patients treated at the Joslin Diabetic Clinic in 1930, 1931 and 1932. Cases were chosen in which the symptoms and signs suggestive of neurologic disturbance were not obviously due to conditions other than diabetes. At first only cases generally designated as instances of neuritis were taken, but later, as it became evident that the condition in these cases blended into other somewhat similar conditions, cases of other types of neuropathy were observed so that the significance and the relation of the conditions to neuritis proper might be studied.

*Grouping of Types of Cases*—I have divided the series of cases into four groups, according to the nature of the manifestations: (1) hyperglycemic type, 34 cases, (2) circulatory type, 27 cases, (3) degenerative type, 45 cases, and (4) neuritic type, 120 cases. This classification was made not to establish a new nomenclature but purely for the purpose of this study. The term diabetic neuritis has gained significance, however vague, through long usage, and it conveys meaning to physicians in many countries. 1. The first group comprises cases in which neuritic symptoms (usually with no signs other than tenderness of the nerve or muscles affected) were associated with an abnormally high sugar content of the blood, disappeared within a few days after the initiation of adequate diabetic treatment and did not recur if the diabetic regimen was followed. 2. The second group includes those cases in which there was considerable circulatory deficiency in the legs and, in addition, pain, paresthesia or signs such as hyporeflexia and hypesthesia. 3. The third group is composed of cases in which rather mild neuritic symptoms and signs began insidiously and tended to progress slowly over a period of years. This group includes cases with such findings as sluggish pupillary reactions and hyporeflexia. Occasionally the neuropathy involved structures which by their nature drew attention to them, as in cases of involvement of the bladder. 4. The fourth group embraces the cases in which there were definite manifestations of neuritis, usually with relatively severe symptoms or signs, such as paralysis. The onset was relatively acute, and improvement usually took place within a few weeks or months.

## 1. HYPERGLYCEMIC TYPE

Thirty-four cases of the hyperglycemic type are reported on here. No attempt was made to include all those cases observed during the thirty-two months of this study. The cases were selected at random from those encountered. They seemed to show the various features of the condition and to be fairly representative of the group as a whole. The cases were segregated because there were neuritic symptoms (with

no signs of neuritis except tenderness), which disappeared simultaneously with the reduction of the glycosuria. In 2 of the 34 cases the diabetes was controlled with great difficulty, and it was a matter of months before it was well regulated and the symptoms were relieved. In these 2 cases there were other features that rendered them a little atypical. In 1 (case 5,932) the patient had pulmonary tuberculosis, and signs of neuritis developed about the time the pain disappeared. In the second case (case 6,659) pain and tenderness of various nerves and muscles developed immediately after the extraction of an abscessed tooth, with an exacerbation of symptoms after the extraction of a second abscessed tooth, and the patient did not become symptom-free until five months after the second episode. Incidentally, the neuritis became much worse when pills of ferrous carbonate were given, possibly owing to constipation. In both of these cases the patient was young and had severe diabetes. Even with treatment there were hyperglycemia and glycosuria, so it is not surprising that pain persisted so long.

*Site, Symptoms and Signs*—The site of this type of neuritis<sup>3</sup> varied little. In 26 cases (76.5 per cent) it involved only the legs. In the other 8 cases, there was more or less generalized involvement, either of the arms and legs together or of the entire body. The outstanding symptom was pain, especially at night when the patient was in bed. Some patients had pain only at night, and in most instances relief followed pacing the floor. Cramps, again especially at night, were at times the outstanding symptom. Sometimes the pain was transitory and sharp, and at other times, merely a dull ache. Once it was described as "a tearing of the calf muscles." This nocturnal type of pain is often referred to circulatory deficiency, but that did not seem to be true in these cases. At least, there was no obvious circulatory deficiency, and many of the patients were young and had little if any arteriosclerosis. Sometimes only paresthesia was present. This was manifested by coldness, numbness or prickling. Hyperesthesia to touch has been noted, as has a sensation of weakness, although I did not observe muscular paresis in any case. Some patients became nervous, irritable or depressed, but only 1 patient (case 6,659) showed a definite psychic upset. Tenderness of the nerves and muscles was not infrequently noted, and in some instances there was hyperesthesia. In 1 case (case 10,416) there was hypesthesia of the left side of the body, with no other evidence of cerebral vascular accident. Paresthesia of the left side of the body had been present for the six months during which the patient had had diabetes, and yet it disappeared on the second day after diabetic treatment was started. A decrease of the tendon jerks was noted in 5 cases, in each of which there was a combination of two or more of

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3 For convenience I shall refer to each type as neuritis.

the types described. In each of these cases symptoms were relieved at once by diabetic treatment.

*Fever and Blood Picture*—A tabulation of the temperature was not made for this group, although routine readings of temperature were noted for each patient, no one of whom had a noticeable febrile reaction not accounted for by other conditions. A white blood cell count was made in 6 cases, and the values ranged from 6,450 to 10,350. In 5 cases a blood smear was made. In 1 of these cases there was an abnormality, presumably due to an acute pulmonary infection of which the patient died in a few days. In another case (case 10,945) there was 7 per cent eosinophilia without known cause. In the other 3 cases smears were normal.

*Pathology*—Prompt recovery prevented a study of the pathologic process.

*Etiology*—Discussion of the etiology of each type separately necessitated considerable repetition, but it seems worth while as an aid in determining the various factors at work.

*Sex and Age*—Of the 34 patients, 23 were women and 11 (32.4 per cent) men. The age at the onset of the neuritis varied from 18 to 70 years, with an average of 46.4 years. Nine patients (26.5 per cent) were less than 40 years old, and 7 (20.6 per cent) were below 30 years of age.

*Severity and Duration of the Diabetes*—The diabetes was not always severe, but at the time symptoms appeared it was always uncontrolled. In 10 cases (29.4 per cent) the diabetes was mild, and in only 3 (8.8 per cent) was it severe. Thus, one sees that even though a diabetic patient has considerable glycosuria and neuritic pain, by adhering to treatment he may be relieved of the pain within a few days and may prove to have mild diabetes, requiring little or no insulin. Several of the patients had symptoms of neuritis before the apparent onset of the diabetes. This is not surprising, since marked hyperglycemia and glycosuria are often unassociated with hunger, thirst and polyuria. Two of the patients had had diabetes for thirteen years before neuritis began. The average duration of the diabetes prior to the appearance of neuritis was three and three-tenths years.

*Dehydration and Acidosis*—The clinical appearance of the patient or a gain of several pounds in weight within the first few days of treatment was used as a measure for dehydration. By this standard it was noted that dehydration was present in 10 cases (29.4 per cent). Furthermore, as judged by the clinical appearance of the patient or the finding of acetone bodies in the urine, acidosis was present in only 9 cases (29.5 per cent). In 22 cases (64.1 per cent) there was neither dehydration nor acidosis. Such evidence suggests that neither of these

factors is essential for the production of the symptoms. Furthermore, it is well known that whereas in many cases diabetic coma is accompanied by severe pain, in others there is none, even though acidosis and dehydration are marked. Recently I closely questioned 9 diabetic patients with marked dehydration, 4 of whom had definite acidosis (in 2 the carbon dioxide-combining power of the plasma was below 20 volumes per cent), and none had the slightest symptom of neuritis.

**Cholesteremia.** I used the cholesterol content of the blood as an index of the disturbance of fat metabolism, especially in the patients without acidosis. Such an analysis was made on 13 of the patients, 6 (46.2 per cent) of whom had hypercholesteremia. Such a percentage is not high, for in all these patients the diabetes was uncontrolled. The lowest cholesterol value was 145 mg., the highest, 305 mg. (230 mg. being the maximum of normal), and the average, 225 mg. Two factors tend to exclude hypercholesteremia as a cause of the symptoms. First, more than half the patients tested showed normal cholesterol values. Second, the level of cholesterol in the blood changes slowly under the treatment at the clinic, and these patients obtained relief within a few days after treatment was instituted.

**Accessory or Nondiabetic Factors.** Foci of infection were present in 25 per cent of the cases, but relief from the symptoms was not postponed until the infection was removed. Arteriosclerosis is so prevalent in diabetic persons that its high incidence is not significant. In 6 cases (17.77 per cent) there was no arteriosclerosis, and in 3 others there was only a slight degree of it. A previous dietary deficiency had not existed in the 5 cases in which there was specific questioning about this. Achlorhydria was present in only 2 of the 10 cases in which a test was made, and in these 2 there was no other evidence of pernicious anemia or combined system disease. Tuberculosis was present in only 1 case. The prompt relief of symptoms tends to exclude all these factors as causative agents. No other possible causes were discovered.

I cannot say that hyperglycemia alone causes the symptoms, for it is often present in diabetic persons who have no symptoms and whose immunity is unexplained. Nevertheless it was the only factor noted in all cases, and correction of it was followed immediately by a disappearance of the neuritic symptoms. Furthermore, it is recognized that in diabetic persons pain of a different nature from that described here is often worse when the value for blood sugar is high and less severe when the diabetes is controlled.

**Prognosis.**—The criteria for the selection of these cases necessitated a good prognosis. However, it is interesting to note that several patients who had had symptoms for more than a year obtained prompt relief when diabetic treatment was instituted. One patient (case 10,562) had had pains and cramps in the calves of the legs for the preceding seven

years, and yet twenty-four hours after the excretion of sugar in the urine decreased below 1 per cent all the symptoms stopped. In another patient (case 11,036) the right ankle jerk, which had been sluggish, became definitely more active within three days after the patient became aglycosuric. In all but 2 of the cases the diabetes was fairly easily controlled, and in only these 2 was relief from the pain delayed. In 31 of the 34 cases the symptoms disappeared within a week after the initiation of diabetic treatment. One patient (case 11,092) was not so fortunate, as his symptoms lasted sixteen days, but he had a carbuncle and considerable diabetic acidosis. The average duration of symptoms after treatment was begun was three and six-tenths days. The future course of these patients should prove interesting and instructive. Sufficient time has not elapsed for me to say what this hyperglycemic pain may signify. However, 4 patients have subsequently shown evidence of real neurologic disorder. One patient (case 9,913) nine years after the first attack of hyperglycemic symptoms had advanced circulatory deficiency of the legs, and there was absence of the tendon reflexes. Another (case 5,932), a boy of 18 years, although essentially symptom-free, had sluggishness of the knee jerks and right ankle jerk and absence of the left ankle jerk. Sensitivity to pinprick diminished on the anteromedial surface of the lower portion of the legs. Another patient (case 9,759) had neuritis with definite signs, although she had been aglycosuric and had been receiving insulin during the interim between the disappearance of the hyperglycemic symptoms and the onset of the neuritis. Incidentally, during the same period the pulsation in the dorsalis pedis arteries diminished practically to the point of absence. Another patient (case 9,765) experienced an almost identical course, including the circulatory change, in a period of ten months. The relatively slight increase in the duration of the diabetes in the 3 last mentioned cases is hardly sufficient to explain the changes.

*Treatment*—The treatment was the regular regimen for diabetes. Relief is so prompt that other treatment is usually unnecessary. Heat, salicylates or hypnotics may be used if necessary. Massage was very effective in 1 case (case 6,659). The general condition of the patient and foci of infection should be given the attention required.

## 2 CIRCULATORY TYPE

To study this type, I have taken at random 27 cases. The frequency of the condition is illustrated by the large percentage of diabetic persons who have sufficient circulatory deficiency to warrant amputation of the legs. Labbé (1931) mentioned certain symptoms and signs observed in this condition.

One can quickly dispose of this type by stating that in all essential features it resembles the degenerative type. The onset, symptoms and

signs, course, site, etiology, age at onset, prognosis and treatment are the same in both groups, with few exceptions. The patients with circulatory deficiency occasionally have intermittent claudication, which was not present in the patients with the other type of neuritis. Parts of the body with no evident circulatory deficiency were affected in patients in this group, and those with degenerative nerve lesions in other parts of the body occasionally had sluggish circulation of the lower part of the legs. I believe that a separation of these two types is not indicated, that they should be grouped as one under the degenerative type. Provision for poor circulation of the feet can be made easily by prescription of Buerger's exercises and more careful attention to the feet to prevent and treat lesions which might receive surgical intervention. I shall therefore combine pertinent data on these 27 cases with those of the degenerative type.

### 3 DEGENERATIVE TYPE

Of the many cases of this type encountered I have used 45 for this study. Among these are cases illustrating the various features of this type of neuritis and also cases which disclose the difficulty of segregating some cases of this type from those of the hyperglycemic and neuritic types. These cases represent the type of neuropathy from which such a large percentage of diabetic persons suffer. They include the type of cases in which the routine examination discloses hyporeflexia or areflexia of the tendons or sluggish reactions of the pupils. Mild pain or paresthesia is usually acknowledged if one questions the patient, but the symptoms of neuritis are rarely a major complaint. The onset is insidious and the course prolonged. The superimposition of other conditions may complicate the picture, so that a decision as to the type of neuropathy is reached with difficulty.

The earlier symptoms in case 8,166 suggested that the patient might have had real neuritis, but at the time of examination the mildness of the symptoms, the minor signs and the ten years' duration of the neuritis suggested rather a degenerative condition.

*Site and Symptoms*—In 18 cases (40 per cent) there was involvement only of the legs, in 6 cases, of the arms and legs alone, in 10, of the pupils and legs, and in 2, of the pupils alone. In the remaining 9, there was generalized involvement. The predominant symptoms were pain, cramps and paresthesia. All symptoms were worse at night, usually markedly so, and were increased occasionally with fatigue. The pain was at times dull and at other times sharp, steady or momentary. Burning pains were complained of less among this group than among those with the circulatory type. One patient (case 10,100), in addition to neuritis of the leg, with a sense of vibration and a sensation as of "cold water poured down the bone," complained of neuralgia of the gums of two years' duration. The left pupil reacted sluggishly to light. Another

patient complained of a binding feeling around the calf, especially at night, so severe that he could not lie still. Fifty-seven and one-tenth per cent of the patients had pain of some type, and 55.3 per cent had paresthesias. The paresthesias included numbness, prickling, burning, coldness and, rarely, generalized itching. One troublesome and unexplained symptom, occurring in case 9,643, was numbness, as if the hands and feet were asleep. There were no other symptoms, and the only sign was absence of the knee jerks, although the ankle jerks were normal. There was no obvious circulatory deficiency or anemic condition. The gastric free hydrochloric acid showed 64 degrees of acidity. There was moderately advanced arteriosclerosis. In case 11,075 there was intractable numbness of the hands. There were also pain and tenderness of one arm and rectal incontinence, apparently dependent on a relaxed sphincter. In case 6,331 there were slight urinary incontinence and absence of the right ankle jerk. The cases in which there was loss of control of the sphincter will be discussed later.

*Signs*—The neurologic observations included sluggishness or absence of the tendon jerks, weakness of the legs or of isolated groups of muscles with or without atrophy, weakness of the anal sphincter, tenderness of the nerves and muscles, hypesthesia, anesthesia, an abnormal pupillary reaction and, in 1 case, a positive Romberg sign. The hypesthesia was noteworthy. In 1 case in which there were no symptoms there was generalized hypesthesia, most marked on the lower portion of the left leg, and there were sluggishness of the left ankle jerk and absence of the right ankle jerk. One patient (case 10,528) did not show a noticeable decrease in sensitivity to pinprick, but she experienced almost no pain when the surgeon cut and probed the infected foot. The signs in 1 case were so striking, albeit rare, that I report it as follows:

CASE 10,451—A 56 year old woman, with moderate arteriosclerosis and diabetes of fourteen years' duration, noted paralysis of the muscles elevating the foot. The ankle joint became swollen but not tender. Bits of bone were painlessly extruded from the toes. The lesions would heal but recur, or new ones would develop. The ankle joint became useless and instable. The process then involved the other ankle and foot. One ankle improved, the cutaneous lesions healed, and the foot drop became less noticeable. Two years after the onset I observed a rather typical, painless Charcot joint of the ankle, in addition to chronic osteomyelitis of the foot of an unusual type and without obvious etiology. There was partial left foot drop, with hypesthesia of the lower portion of the legs, most marked in the distribution of the external peroneal nerve. The knee jerks were normal, but there was absence of ankle jerks. The Wassermann test of the blood and spinal fluid gave negative results, but the colloidal gold curve resembled the type associated with dementia paralytica. Leprosy seemed an unlikely cause. The similarity of the disturbances produced by syphilis and diabetes and the absence of proof of the former in the history, the physical examination and the serologic study led me to consider this tentatively as a diabetic process of a neurologic trophic nature.



In 13 (28.9 per cent) of the 45 cases the knee jerks were normal, in 8 (17.8 per cent) there was absence of the patellar reflexes, and in 24 (53.3 per cent) there was absence of one or sluggishness of one or both reflexes. The ankle jerks were normal in only 7.3 per cent of 41 cases, and in these 3 cases there were other definite signs. Sensitivity to pinprick was normal in 55.6 per cent of 27 cases and decreased in the remaining 44.4 per cent. Sensation to touch, heat and cold corresponded to sensitivity to pinprick in the cases tested, but these tests were not employed frequently. In general, sensitivity, when abnormal, decreased progressively from the thighs down to the feet, but usually the distribution was patchy, so that one might strike sensitive points in areas otherwise insensitive. In case 5,112 there was sudden numbness of the dorsum of the left foot, with loss of sensation of pain and light touch. The pulsation in the dorsalis pedis artery was questionable. The following day the pulse was felt, and sensation was normal. I believe that sensitivity decreases with decreasing circulation and increasing arteriosclerosis, although there are a number of exceptions to this rule. Position sense of the great toe was tested in 25 cases and was decreased in only 3.

*Pathology*—The pathologic process was not studied in these cases. Many of the cases reported in the literature seem to fall in this group of the degenerative type, and I shall mention here the pathologic process described in the literature. Changes were noted in the spinal cord by nine authors,<sup>4</sup> in the cord and nerves by eight,<sup>5</sup> in the peripheral nerves by eight<sup>6</sup> and in the posterior roots by three.<sup>7</sup> The early report and summary by Auché (1890) and the recent one by Woltman and Wilder (1929) are good. In the latter article are transcribed the histories of 42 cases reported in the literature, in 24 of which there was degeneration of the peripheral nerves, in 16 degeneration of the funiculi, in 8 changes in the anterior horn and in 4 intramedullary degeneration of the posterior roots. Auché described a case of parenchymatous neuritis with considerable myelin degeneration and changes in the axis-cylinder in isolated nerve fibers. The process seemed chronic and progressive, involving first one fiber and then another, the first affected often showing sufficient

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4 Minor (1889) Lichtheim (Sandmeyer, 1892) Williamson (1898, 1904) Van Leyden and Goldscheider (1895) Nonne (1896) Souques and Marinesco (1897) Naunyn (1906) Schweiger (1907) Root and Rogers (1930)

5 Leichtentritt (1893) Van Leyden (1893) Bonardi (1897) Findlay (1902) Ossokine (1902) Bramwell (1907) Marinesco (1901) Woltman and Wilder (1929). In the last two reports chief stress was laid on lesions of the peripheral nerves.

6 Pryce (1887, 1893) Nonne (1889) Auché (1890) Eichhorst (1892) Fraser and Bruce (1895, 1896) Hensay (1897) Fleming (1897) Wittmaack (1907)

7 Williamson (1904, 1924) Hensay (1897) Schweiger (1907). According to Wright (1931)

regeneration so that the function of the nerve seemed never to be lost Auché noted normal nerve tissue proximal to markedly diseased nerve tissue and concluded that the changes in the nerve were not secondary to changes in the spinal cord Pryce (1893) was struck by the association of arterial disease with the degeneration in the nerves Marinesco (1901) also commented on the thickening of the walls of the intraneural arteries Woltman and Wilder (1929) noted slight changes in the cord and marked changes in the nerves These changes consisted of patchy degeneration of the nerves, with myelin disintegration and at times infiltration by lymphocytes, polymorphonuclears and fat-laden cells The lesions were more marked in the peripheral than in the proximal parts of the nerves, an observation described also by Auché Woltman and Wilder noted sclerosis of the intraneural vessels and concluded that this arteriosclerosis was a most important etiologic agent In 1 of their cases regenerated fibers were observed Similar regeneration was reported by Nicolescu and Raileanu (1926, 1927) in their description of the pathologic changes in the brain in diabetes Warren (1930) studied the pathologic process in many diabetic patients, a large number of his nerve specimens having been obtained from limbs amputated because of diabetic gangrene The pathologic process in the nerves was not very conspicuous but the small peripheral branches of the nerves were not studied Sclerosis of the intraneural arterioles and occasionally myelin degeneration were observed

*Etiology*—Sex and Age Two thirds of the patients were women, and this may be explained by the fact that the women were more nervous and probably drew attention to their neuropathy more often than did the men The age at the onset of the neuritis varied from 40 to 77 years, with an average of 59.2 years In the cases of the circulatory type the average age was 58.1 years, and the youngest patient was 40 years old

*Diabetic Factors* In this group the average duration of the diabetes before the onset of the neuritis was four and five-tenths years, but sometimes the neuritic symptoms preceded the apparent onset of the diabetes In 6 cases the average duration of the neuritis prior to the diabetes was four and five-tenths years The record for case 10,582 is interesting The patient was admitted to the hospital with an occluded femoral artery and a neuritic condition of the diabetic type However, throughout the first stay at the hospital tests of the urine and blood did not reveal evidence of diabetes, and my associates and I concluded that the neuritis, which we had thought rather characteristic of diabetes, was of a different etiology Within a short time the patient returned with an inflammatory condition of the foot, and under this added strain the diabetic condition became evident, with a blood sugar content of 0.23 per cent This patient had had neuritis for twelve years before the presence of diabetes was proved, although slight glycosuria had been noted previously One may

contrast this with case 5,866 in which diabetes was present for twenty-four years before the neuritis was noted. In 18 cases (41.9 per cent) diabetes had been present for one year or less. Thus, there is no evidence to prove that long continued diabetes is necessary for the production of these nervous changes. The diabetes was mild in 31 cases (68.9 per cent) and severe in 3. Similarly, in 69.7 per cent of the cases the diabetes had previously been at least fairly well controlled, as judged by the tests of the urine cited by the patients. The values for cholesterol in the blood were not so good, as illustrated by the fact that in 7 of the 13 cases in which tests were made the values were above the maximum normal level, the average for the 13 cases being 236 mg. In the cases of the circulatory type the average value for cholesterol in the blood in 9 cases was 267 mg., which is 16.1 per cent above the maximum normal value.

**Arteriosclerosis.** By examination of the arteries I detected moderate or advanced arteriosclerosis in 41 of the 44 cases in which there was a record of this condition, and in 1 other a condition of the foot required surgical intervention, which in diabetic persons usually implies at least moderate vascular disease. Angina pectoris was present in 7 cases (15.6 per cent), a condition of the feet requiring surgical intervention in 19 (42.2 per cent) and apoplexy in 4 (in 1 of which it was questionable). The circulation in the legs seemed normal in only 20 per cent of the patients, and it was very deficient in 35 per cent. Of the entire group arteriosclerosis was present in every case, and in 95.5 per cent there was evidence of moderate or advanced vascular disease.

**Dietary Deficiency.** Fourteen patients questioned about their diets prior to the neuritis gave no history of a definite deficiency, although 1 patient (case 10,582) might not have eaten as much meat, fresh fruit and green vegetables as is usually considered normal. No deficiency of the nature of pernicious anemia was detected, although achlorhydria was present in 5 of 11 patients tested. Of the other 6 patients, only 1 had less than 25 degrees of free acidity, and the average for the 11 patients was 30.5 degrees. Among the patients with the circulatory type, only 1 of 7 tested had achlorhydria.

**Alcohol, Foci of Infection and Syphilis.** Of the 41 patients for whom there was a record of the consumption of alcohol, only 3 (7.3 per cent) had imbibed any. The incidence of foci of infection was also slight (11.6 per cent), but it is to be remembered that in many cases abscessed teeth may have been removed prior to my examination. Syphilis was present in none of the 45 cases.

To summarize the etiologic data, I may say that the only two factors, primary or contributory, which I have observed are the diabetes and the vascular disease. It seems that some obscure feature of the diabetes

and not simply hyperglycemia, is at fault. The abnormality in the cholesterol content of the blood suggests a possible factor in the production of this neuropathy.

*Prognosis*—The chronic and at times progressive nature of the condition precludes a good prognosis. The signs are likely to remain, if not to progress, in spite of the best treatment, and even the symptoms linger for months or years, although they may at times decrease considerably in severity. In some patients in whom the diabetes has been inadequately controlled relief from symptoms is moderate and rather prompt when they adhere to the diabetic treatment. Nine patients received relief in this manner, although in 4 the alleviation was slight. Two patients always paid by an increase in symptoms for any relapse in treatment. Amputation on account of markedly deficient circulation ended the symptoms in 1 case, but the absence of the knee jerk in the remaining leg testifies to the presence of the neuropathy. One patient received much benefit from Buerger's exercises. One patient (case 8,965) wrote that after two and one-half years she has had no more neuritis, and another (case 9,860) was relieved in one year, but in neither instance have I been able to examine the patient to see if the absence of the tendon jerks and other signs have been restored to a normal state. In case 1,217 the symptoms began when the patient was aglycosuric, according to her, and progressed during the three years prior to the time I saw her, yet rest and heat afforded relief. In 3 cases the neuritis has lasted ten years or more. One of these (case 8,166) is interesting. The manifestations of neuritis consisted of pain, paresthesia, weakness and areflexia in the legs. During the past several years the carbohydrate content of the diet has been gradually increased. In the past three years the neuritis has improved definitely. The symptoms and weakness disappeared, and the patellar reflexes have returned to the point where both can be obtained without reenforcement, and this in spite of hyperglycemia and a cholesterol value 41 per cent above the maximum normal. In case 10,135 there was also a lessening of signs. In a period of ten months during which the patient was treated with insulin, one knee jerk, which had been very sluggish, became practically normal and the paresthesia ceased. In case 9,643 there was absence of knee jerks, which later were partially regained. In case 6,331 there was absence of the ankle jerk on the right side but a normal ankle jerk on the left, the side on which there was hemiplegia. The average duration of the neuritis in the 45 cases has been three and five-tenths years. In the group of the circulatory type improvement in tendon jerks was noted in 3 cases (cases 1,696, 2,843 and 9,287). The average duration of the neuritis in this group was four and four-tenths years. Obviously this short duration is due at least partially to the fact that in general the patients have been observed over a period of only two and one-half years or less and

some were observed for the first time only a few months before this study was completed

*Treatment*—Persistent treatment of the diabetes should be demanded. One should not expect too much, because in 69.7 per cent of these cases the neuritis has appeared or persisted in spite of apparently well controlled diabetes. However, in a number of cases quite a little relief was obtained after the institution of diabetic treatment. Observation of roentgenograms of the legs of some diabetic patients makes one both discouraged and hopeful. The calcification of the arteries is often extreme and completely obliterates the lumen, but at the same time one sees evidence of smaller collateral arteries developing to care for the area formerly deprived of its blood supply. Buerger's exercises have given fairly good results in some cases and should be tried. In 19 of the cases of the circulatory type I know the effect of these exercises. Five patients obtained much relief, and 8, moderate relief, a total of 68.4 per cent. Only 3 patients failed to receive apparent benefit. Even these patients should continue the exercises, because in time sufficient collateral circulation may develop. Sedative measures, similar to those used for hyperglycemic symptoms, may be employed for the temporary relief of pain, but one must be more careful in prescribing drugs, because the condition persists for a long period. Furthermore, the vascular disease, with hypesthesia and susceptibility of the tissues to injury, makes it essential that extreme care be used in applying heat. In the hospital I have used an electric baker, regulated by a nurse who understands both the apparatus and the condition of the patient. Warm baths are sometimes recommended for the relief of pain, but it is well for a young person with sensitive skin to test the temperature of the water. Hot water bags, especially of the chemical type, are looked on with disfavor. Meticulous care and cleanliness are essential in trimming toe-nails, calluses or corns. In many cases this is better left to a skilled chiropodist who understands the diabetic and vascular conditions. One homely remedy, occasionally effective for patients with low blood pressure and impaired circulation in the legs, is a glass of water at bedtime. Sometimes it permits a night of uninterrupted sleep.

#### 4. NEURITIC TYPE

In this group belong the cases ordinarily described as cases of diabetic neuritis or diabetic tabes. I have observations on 120 such cases to present. Some probably would not be classified as cases of neuritis by many physicians, but they have some features in common and they serve as examples for purposes of discussion. In many cases the same features were present as those exhibited in cases in the three preceding groups, but this is not surprising when one considers the two apparent causes (hyperglycemia and arteriosclerosis) operating in the former groups. Certain other manifestations in the group may represent merely an exten-

sion or exaggeration of the processes in the preceding groups, but the clinical picture and the course of the disease suggest that the condition in these cases is possibly different, and I have put them in a separate group for study, so that conclusions drawn may not be false owing to improper selection. In this group are cases of neuritis possibly resulting from causes other than diabetes and its related concomitants, but I believe that even in these the presence of the diabetes had an effect on the type or degree of neuritis produced. In general, the condition in cases of the neuritic type differed from that in cases of the degenerative type in that the neuritis was usually a cause of real difficulty, the onset was often acute and the neuritis tended to improve markedly within a reasonably short time. In some cases the patient improved rapidly and was free from both symptoms and signs. This contrasts sharply with the chronic course and absence of complete cure in the former group.

*Incidence*—It is difficult to determine the incidence of diabetic neuritis because it is difficult to decide what constitutes neuritis. Furthermore, contact with the patient must be maintained from the onset of the diabetes until death, because the neuritis, unlike the diabetes, is at times transient. One author reported the incidence of pain, another the absence of knee jerks and another the frequency of abnormal knee jerks, and another made a more general statement as to the frequency or rarity of the condition.

Bouchard (1884) noted absence of the patellar reflexes in 28.5 per cent of diabetic patients, Auerbach (1887) in from 35 to 40 per cent, Maschka (1885) in 30.6 per cent, Eichhorst (1892) in 18.8 per cent, Grube (1893) in 7.6 per cent, Williamson (1924) in 49 per cent and Melander (1931) in 3.8 per cent. Auché (1890) believed that diabetic neuritis was not a rare complication in diabetes. Pitres (1902) reported 1 case of diabetes in which there was absence of the pupillary reflex and 20 of 32 showing weakness or absence of the patellar reflexes. Williamson (1905) reported decreased vibratory sensitivity in 15 of 45 diabetic patients. Kraus (1922) noted abnormal knee jerks in 40 per cent of 450 such patients. Stewart (1925) stated that the nervous system is involved in 50 per cent of diabetic persons. Von Noorden and Isaac (1927) stated that 31 per cent of diabetic patients have pain, but Woltman and Wilder (1929) noted pain in only 10 per cent and paresthesia not accounted for by arthritis, myositis or trauma in 10 per cent. Wendt and Peck (1931) mentioned persistent pain in 5 per cent of their cases. Murphy and Moxon (1931) reported neuritis in 0.6 per cent of their cases. Sevinghaus (1931) noted pain in 49 per cent and reduced reflexes in 57.3 per cent of his diabetic patients especially examined for these conditions.

This high incidence of neurologic derangement in 1931 seems to cast doubt on the assertion of Melander that the administration of insulin

has decreased the incidence of abnormality of the reflexes by enabling persons with diabetes to remain in better general condition, although he did use absence of the reflexes rather than mere abnormality of the reflexes as his guide. The incidence of diabetic neuritis in my cases was arrived at in two rather inadequate ways. Sluggishness or absence of one or more of the knee jerks or ankle jerks probably gives a fair idea of the presence of the degenerative changes of the nerves, but it includes such an abnormality due to any cause. It indicates the presence of the neuropathy only at the time of the examination and fails to include those cases in which such a neuropathy develops later. Among 461 unselected cases of diabetes, normal knee jerks and ankle jerks were noted in 252 (54.7 per cent), except that the left knee jerk in 1 case was hyperactive. In all other cases there was a decrease of one or more of the four tendon reflexes. In no case was there hyperactivity of the tendon jerks as a whole, in only 2 cases were there hyperactive knee jerks, and in both cases there was absence of the ankle jerks. The knee jerks improved in six months in 1 case, and in another the ankle jerks improved in seven months. There was absence of all the knee jerks and ankle jerks in only 22 cases (4.8 per cent). The second method of determining the incidence of neuritis has its faults also. This study extended over a period of two and one-half years. I noted real neuritis in 25 of 1 000 consecutive cases observed for the first time in the period of this study. Neuritis may appear later in many more of the 1,000 cases, but so far the incidence has been only 2.5 per cent.

*Site*—I had 120 patients, 1 of whom had two apparently unrelated attacks of neuritis. The site of the neuritis in these 121 cases was as follows

	Cases	Percentage
Legs	81	66.9
Arms	8	6.7
General involvement and other special sites	32	26.4

The neuropathy may involve almost any part of the body from the pupils to the feet. The optic, the oculomotor, the facial, the auditory and the recurrent laryngeal nerves have all been affected directly or indirectly, as evidenced by abnormal function of the structure innervated. I have mentioned 1 case in which the condition simulated ureteral colic. Disturbance in the bladder, as revealed by incontinence or by retention with paralysis of the wall of the bladder, has been observed. Cases of abdominal symptoms have been observed. The predominance of involvement of the legs is striking and is in accord with previous reports.

*Clinical Picture*—The student of diabetes is apt to forget the ordinary significance of certain neurologic signs. He sees them so often in diabetic patients that he becomes accustomed to changes that would greatly perturb the student of other diseases, who knows these signs are often

of serious portent in nondiabetic persons. To describe the clinical picture of diabetic neuritis, it is necessary to report several cases at least briefly. Others will be described because it is a moot point whether or not the condition was neuritic, and I wish to present them for consideration and discussion. To mention all the symptoms and signs met with in this condition would confuse rather than clarify any ideas of the disease, for they are protean and may simulate many other diseases of the nervous system. It is well to remember that pain (especially at night), paresthesia, decreased activity of reflexes and paresis are the most frequently encountered features and that in the great majority of cases the legs are affected. Even considering the defectiveness of ordinary observation, memory and subsequent description, one is impressed by the vagueness of the condition. It seldom involves only the area innervated by one nerve, and often it does not involve all this small area. Feiling (1921) and Hyslop and Kraus (1923) implied that multiple neuritis and lead neuritis may also be diffuse and cause changes in the central as well as in the peripheral nervous system. The person with diabetes who can definitely outline the boundaries of the area affected by the neuritis is rarely seen. Even the time of onset is not always well marked, although some patients describe a definite, acute onset of symptoms. The very vagueness of the descriptions and the widespread area affected by symptoms or signs suggest a diffuse and patchy involvement of the nervous system, an insidious process rather than an isolated and sharply demarcated one. It is difficult to conceive of true neuritis, involving all the fibers of a nerve trunk, causing most of these neuropathies. It is not unusual to note an abnormal tendon reflex in one leg whereas the patient complained of neuritis of the other leg. Another patient may complain of discomfort in only one leg and yet on close questioning acknowledge symptoms in the other also. The indefinite nature of the condition may be explicable on the basis of two conditions, neuritic and degenerative, affecting the nervous system simultaneously. It is hardly fair to interpret all the changes as being due either to the more acute process or to the chronic degenerative one. It seems definite that at times there is acute neuritis superimposed on a chronic condition. The former responds well to treatment, yet slight symptoms or signs remain, and I am inclined to think that these are due to the chronic condition and are dependent on a different cause from that of the neuritis itself. For example, in case 9,468 there was acute neuritis with foot drop which disappeared within six months. Yet two years later the patient still showed change in the reflexes. I interpret the foot drop and the change in the reflexes as separate conditions. The patient certainly views the two conditions differently. He says that he had neuritis but that now he is cured and I am inclined to agree, although I believe that now he has a diabetic neuropathy, though of a somewhat different nature.



CASE 1,930—A woman of 35 years began to have pain and paresthesia. The pain was very severe and shooting and was felt over the entire body. The paresthesia was described as numbness of the toes, as if there were cotton under them. Two months after the onset the patient consulted me and was given the usual diabetic treatment for patients who are not admitted to the hospital. Diabetes was so severe as to be controlled with great difficulty, but the patient stated that there had not been much glycosuria until the neuritis made the diabetic condition worse. Six months after the onset the neuritis was so severe that the patient was admitted to the hospital, but it was another three months before improvement became definite. A year after the patient was admitted to the hospital the neuritis was much better, although another year elapsed before the patient considered herself cured. Three and a half years after the onset of the neuritis, physical examination revealed a sluggish right knee jerk, absence of ankle jerks, soreness of the calves and hypesthesia of the lower part of the legs. At this time the patient was 39 years old, had moderate arteriosclerosis and had had diabetes for more than eleven years. The treatment in this case consisted of treatment of the diabetes, rest, application of heat, removal of abscessed teeth and the addition of liver extract and yeast to the diet.

CASE 3,869—A woman, 59 years old, with moderate arteriosclerosis and diabetes of three years' duration, had neuritis, which began suddenly with severe pain in the left hip, the posterior portion of the thigh and the lower part of the leg, even to the toes. This was associated with cramps in the calves and numbness in the legs. After six weeks, weakness of the legs developed and caused almost complete paralysis. The knee jerks were normal. Gradually, with the routine treatment for diabetes and neuritis, she improved considerably. At the second visit, seven years later, the patient was still troubled with some paresthesia, cramps and weakness of the legs, especially when there was glycosuria. Examination at this time revealed sluggish knee jerks (especially on the right), absence of the left ankle jerk, weakness of the left peroneal nerve and some weakness and atrophy of the left calf and thigh. The circulation was somewhat deficient in the feet, especially in the left foot. The cholesterol content of the blood was normal. In spite of some discomfort and disability the patient had worked well in the past six years. On the third visit, ten months after the second, examination did not reveal particular change, except that the left ankle jerk was elicited at times. The cholesterol content was 250 mg. The neuritic symptoms appeared occasionally, but the application of heat usually gave relief.

In this case there was an acute onset, and the neuritis responded fairly well to treatment at first, but the symptoms and signs persisted to some extent for more than seven years. It is difficult to believe that the patient suffered from neuropathic involvement from two sources, yet the acute onset and severity of the disability, with improvement at first, are in contrast to the relatively mild symptoms and the prolonged course of the condition in the subsequent period.

CASE 4,319—A man, 70 years old, with advanced arteriosclerosis and diabetes of eight years' duration, had a left foot drop, with paresthesia. Two months later he consulted me, but because he felt so well he did not follow the treatment prescribed, even though there was considerable glycosuria. The paresis improved, but severe pain developed in the leg six months after I saw him. The pain occurred only at night and never when the patient was walking. One year after the onset of the paresis the patient returned on account of severe pain and a moderate degree of nervousness and depression. There were sluggishness of the right knee jerk, absence of the left knee jerk and of both ankle jerks, weakness

of the entire left leg except the calf, tenderness of the muscles of the leg and hyperesthesia from the hip and groin to the lower part of the leg, at which level deficient circulation became evident. Seventeen days of treatment in the hospital afforded considerable relief.

CASE 5,390—A man 35 years old, with slight arteriosclerosis and diabetes of five years' duration, was admitted to the hospital with marked glycosuria, which responded well to treatment with diet and insulin. There were no symptoms or signs of neuritis. Abscessed teeth were removed at this time. A few days after the patient became aglycosuric a constant aching developed in his legs, associated with hyperesthesia so severe that even bedcovers caused pain. Numbness and burning of the feet occurred. Seven weeks after the onset of symptoms the patient returned to the hospital on account of the neuritis. Examination revealed absence of the ankle jerks, which had been normal at the time of the first examination. Hyperesthesia was present over the entire body, except on the lateral side of the right thigh. The muscles and nerves from the hips to the feet were tender. In another month he was unable to walk, and he was then admitted to another hospital, from whence he wrote that he was burned while receiving heat treatment, indicating either a change from the previous hyperesthesia to hypo-esthesia or an abnormal susceptibility to heat. While at the other hospital a tonsil became infected. Subsequent to this the patient began to improve, and he was well within ten months of the onset of the neuritis.

CASE 10,925—A 64 year old man with diabetes of seventeen years' duration had neuritis, with pain in the left leg, tingling in the feet and hyperesthesia. The hyperesthesia diminished gradually, but weakness developed. Seven months after the onset the right leg became involved. There was tenderness of the calves and thighs and weakness of the thigh and iliopsoas muscles, especially on the left side. Sensitivity to pinprick was diminished on the anterolateral portion of the thighs, varying in intensity elsewhere. There was absence of the tendon reflexes in the legs. There were moderate psychic instability and depression, obviously exaggerated by the death of his wife, which occurred during the course of the neuritis. Gradually, during the next five months the neuritis improved markedly, especially in the left leg, which became almost normal.

CASE 10,972—A 65 year old woman sought treatment because of neuritis, and it was discovered that she had diabetes. The neuritis began as pain in the thigh and then extended to the foot, being present only at night. Weakness of the thigh was noted when the patient went up or down steps. Examination revealed tenderness only of the internal lower aspect of the right knee. There was absence of the right knee jerk, but the other three tendon jerks in the legs were normal. There was atrophy of the right quadriceps muscle and weakness of the quadriceps and iliopsoas muscle on the right. The neuritis improved within a month after the onset, but a relapse occurred, the pain and tenderness returned, and the weakness of the leg increased so that the patient could not raise the leg to a couch nor could she rise from a sitting position. Psychic depression became marked. In another month the patient was much better and walked  $1\frac{1}{2}$  miles (2.4 Km) daily. Six months after the onset she considered herself well, and the depression had disappeared.

CASE 8,428—A 30 year old man with diabetes of one and two-tenths years' duration began to have slight numbness of the lower portion of the right leg. After about two and one-half weeks this became more noticeable but was still rather negligible. Three days later, as the patient was walking home, slight pain began in the leg and increased in about thirty minutes to such severity that he

called a physician, who recommended the application of an electric pad. Under the soothing effect of the heat, the patient fell asleep, to awake five hours later to find his foot badly burned. Within three days the pain decreased markedly, but he consulted me because of the burn. Examination revealed a queer burn on the lateral surface of the right foot and on the tips of the toes. The skin was dry, hard and discolored, like dry gangrene. There was a slight formation of blisters in spots. The foot was dry and cold, and the pulse was not detectable below the femoral artery, but the other foot seemed just as cold and had a palpable dorsalis pedis pulse. There was slight arteriosclerosis. There was absence of the right ankle jerk, and there was cutaneous anesthesia roughly in the area supplied by the external popliteal nerve but also of the whole foot except a small part of the dorsum. There was absence of position sense of the right great toe. There was tenderness of the external popliteal nerve.

The patient was admitted to the hospital, where readings for temperature of the skin showed lower values for the left than for the right foot, although the latter was colder than normal. The right foot was dry and the left was moist, and by wetting the right foot with a damp cloth I noted that the resulting evaporation lowered the temperature of the skin to the level in the other foot. I concluded that the sympathetic fibers to the right foot were damaged and that possibly a reflex stimulation of similar fibers to the other foot had caused the excessive sweating and lowering of the temperature in spite of uninterrupted circulation through the arteries. Owing to the inactivity resulting from the surgical treatment, foot drop developed on the right side, even though the ankle jerk and position sense had been partially regained, but eleven days of passive and active exercise overcame the foot drop. Gradually sensation returned in the previously anesthetic area. One may regard the whole attack as being due to sudden occlusion of the artery, but why such a sudden onset without demarcation, why the decrease of pain and return of the ankle jerk and position sense within a few days? Why, if the femoral or popliteal artery was occluded, was only the peroneal nerve affected? It seems more likely that neuritis developed in a limb to which the artery had been occluded slowly (about fourteen months previously the dorsalis pedis pulse was present) and that this vascular change played the rôle in the development of the neuritis that arteriosclerosis usually plays in older patients.

*Symptoms*—Pain was present in 83.3 per cent of the cases. The most prominent characteristic was intensification at night and relief when the patient walked. The pain was at times dull, at other times sharp, sometimes continuous and sometimes shooting and momentary. Occasionally the pain was cramplike, burning, crushing or grinding. Usually it was ill defined, but occasionally it was limited to the course of one nerve, such as the sciatic. Of the 20 cases in which there was no pain, there was muscular paresis in 16, paresthesia in 2, optic neuritis in 1 and absence of reflexes in 1, with return of one knee jerk almost to normal in one year. Although frequently causing pain and other symptoms on the anterolateral surface of the thigh, diabetic neuritis differs distinctly from neuralgia paresthetica (Huddleson, 1928) in that the pain of the former is usually worse when the patient is in bed and is often relieved when the patient paces the floor. Paresthesia occurred in 70 per cent of all the cases and was often worse at night. The

paresthesia assumed the form of numbness, tingling, prickling, burning, coldness and a sensation as if the patient were walking on wool. Dizziness was occasionally experienced. Certain special symptoms will be described more fully later.

*Signs*—Tendon Jerks. The most frequent sign was hyporeflexia, or areflexia, which occurred in 75.4 per cent of the cases. Sometimes, as in cases 8,167 and 10,279, the change in reflexes was more marked in the leg less affected otherwise by the neuritis. In general, when a change in the reflexes occurred, it was present in the area otherwise affected by the neuritis, but sometimes there was no change, and in many cases the changes occurred in areas otherwise free from neuritis.

*Paresis*. Muscular paresis, varying from slight weakness to complete paralysis (case 11,044), occurred in 65.8 per cent of the 111 cases in which a record of this sign was made. In each of 30 cases various muscles of the leg were affected. In 31 cases the dorsiflexor muscles of the foot were involved (bilaterally in 1 case), and in 16 of these no other muscles were weak. The quadriceps femoris muscle was involved in 21 cases, in 7 of which there was no other weakness. The hamstring muscles were affected alone in 2 cases and in conjunction with other muscles in 6 cases and the iliopsoas muscle alone in 2 cases and with other muscles in 8. In 3 cases there was weakness of some group of muscles of the arm. In 1 case (case 9,230) there were weakness and atrophy of both arms and legs. The paresis is not detected with ease in all cases. A patient lying in bed may not notice foot drop, and repeated examinations of bedridden patients are advisable, in order that paresis may be discovered promptly and corrected before it has become severe. Some patients suffered falls, some had difficulty in stepping up into a street car or in climbing or descending steps, and some recognized the difficulty by the flapping of the foot when they walked. In case 9,360 syphilis was suspected because of the unsteady and steppage gait, which Charcot (1890) described. At times the paresis is sufficient to incapacitate the patient completely. Atrophy may or may not be present. Occasionally it is marked and at other times slight, sometimes it is well localized and at other times widespread and manifested merely by the smaller circumference of the affected leg. As in case 4,319, paresis may be the initial symptom of the neuritis, and pain may not supervene until several months later.

*Atrophy of Muscles vs Atrophy Caused by Injection of Insulin*. In connection with atrophy of muscles one might consider briefly the atrophy caused by the injection of insulin sometimes observed in persons with diabetes. No connection between this form of atrophy and diabetic neuropathy has been observed. In 1 patient (case 9,832) who had been injecting insulin in the arms and legs for about six years, I noted numerous areas of atrophy, some at sites where the patient said she had not

injected insulin, although the atrophy was in the general vicinity of the injections. The areas of atrophy were said to have appeared regularly overnight in the limb in which the injection was made the preceding day, and the many areas appeared in the course of one month. Furthermore, the husband said that the areas of atrophy appeared only when the skin was prepared with alcohol, never when mercuriochrome or iodine was used. Examination revealed obvious atrophy of the subcutaneous fat, and it did not follow the course of a cutaneous nerve. There were no tenderness or abnormal sensation at the site, no muscle weakness and no abnormality of the reflexes. If atrophy occurred through the medium of nerves, it must have involved only the tiny peripheral branches. The occurrence of all the changes in only one month of the six years during which insulin had been used suggests that possibly a particular supply of insulin was at fault.

*Tenderness*—Tenderness other than hyperesthesia of the skin was noted in 61.2 per cent of the 98 cases in which the condition was recorded. One may contend that neuritis without tenderness does not occur. I do not insist that this is a form of neuritis involving all the fibers of one nerve trunk. I believe it more likely that it is a patchy involvement which is not limited to the peripheral nervous system. In 35.6 per cent of the cases of muscular paresis, which is good evidence of a real neurologic disturbance, no tenderness was present. In other cases, as in the 2 with involvement of the optic nerve, the affected nerve cannot be examined for tenderness or else it does not carry such sensory fibers. Even when tenderness exists, it usually is not limited to the nerve itself but often is just as marked in the muscles.

*Sensation to Pinprick and Touch*. For cutaneous sensitivity the patients were tested only by pinprick and by light touch of the hand. I used the test for sensitivity to heat and cold only occasionally and observed that it yielded results similar to those obtained with the test for pain. Cutaneous sensitivity was tested in 100 of these cases and was found to be abnormal in 51. Hypesthesia was noted in 56.9 per cent of the 51 cases, hyperesthesia in 29.4 per cent and a combination of the two in 13.7 per cent. The area affected is seldom sharply demarcated, and areas of normal sensitivity are interspersed between abnormal areas. In general hypesthesia involving the lower part of the legs is more marked in the lower portion and gradually changes to normal sensitivity at about the level of the knee. I have attributed this in many cases to impaired circulation at the lower level, but often diabetic persons with infections or trophic lesions of the feet and relatively good circulation have greater insensitivity than those with gangrene and poor circulation. This lends some support to the conception that these lesions are at least partially neurogenic, as was suggested by Buzzard (1890) and Lépine (1909). The case reported by Holt (1928) was of this type. However

there are cases with associated gangrene in which no pain is experienced during surgical maneuvers (case 10,582), and rarely one sees a diabetic patient with circulation so poor that amputation is carried out, and yet surgical procedure causes severe pain (case 9,429). McKittick and Root (1929) attributed the trophic ulcers of the feet to pressure, poor circulation and infection rather than to a neurologic cause, but blisters and ulcers on the feet occur at times without an obvious precipitating cause. Some patients (cases 5,361 and 5,390) have had hyperesthesia and also sufficient hypesthesia to burn themselves without noticing the pain. Two other patients (cases 2,411 and 8,428), suffering only from hypesthesia, burned themselves and felt absolutely no pain.

**Position Sense and Ataxia** Considering the lesions in the posterior columns described by many authors, one would expect to find ataxia and loss of position sense frequently, but this has not been true in my experience. I tested for position sense in 82 cases and noted that there was decrease or absence in 13 (15.9 per cent). In 4 of these 13 there was a history of at least a slight consumption of alcohol, and in 1, of syphilis. One patient had pernicious anemia, 1 had secondary anemia and 1 had ocular lesions attributed by the ophthalmologist to syphilis, but there was no other evidence of syphilis according to the history, physical examination or serologic study. There remained 5 cases in which there was no evidence of alcoholism, syphilis or anemia in which there was loss or decrease of the position sense. Ataxia was very rare, in this series it was recorded only four times, for 1 patient with syphilis, for 1 with combined system disease and for 2 who said that they consumed small quantities of alcohol. In the following case the patient was definitely addicted to the use of alcohol as well as being diabetic.

**CASE 5,841**—A 55 year old man began to have severe shooting pains throughout the whole body, especially in the legs and especially at night. Burning sensations supervened. Finally, the patient noticed that he had to watch his feet when he walked. The examination revealed tenderness of the nerves, hyperesthesia of the legs with an indefinite upper level, slight weakness of the flexor muscles of the feet and slight general weakness, slight ataxia and sluggish tendon jerks. Galvanism made the symptoms worse. In eighteen months, with diabetic and general treatment, the patient was able to walk normally, and he seemed to be cured of the neuritis.

**Fever**—An elevation of temperature was recorded in 25 per cent of the 112 cases in which readings of temperature were made. The elevation was usually slight, and the temperature was never high, ranging from 98.8 to 100.6 F. In some cases there were days of normal temperature interspersed between days with fever. Many patients other than the 28 mentioned here had fever due to some obvious cause, but in these 28 cases no cause was found, unless it was the diabetic neuropathy.

*Leukocytosis and Differential Count*—Of the 50 patients for whom a white blood cell count was carried out, 13 (26 per cent) had more than 10,000 white blood cells, and 4 of these also had fever. Ten of the 13 patients had a normal blood smear, examination of the blood smear was not carried out for 2, and for 1 the cell count showed 85 per cent polymorphonuclears. Of the 4 patients with fever and leukocytosis, only 1 had an abnormal blood smear (85 per cent polymorphonuclears). In 47 cases a study of the blood smear was made. Three of the patients had pernicious anemia, and 32 others were normal. For the remaining 12 the cell count was as follows: 3 had 6 per cent eosinophilia, 3 had 3 per cent eosinophilia, and the other 6 had, respectively, 66 per cent lymphocytes, 56 per cent lymphocytes, 42 per cent lymphocytes, 85 per cent polymorphonuclears, 56 per cent polymorphonuclears and 49 per cent polymorphonuclears. I have no explanation for the slight eosinophilia. Foci of infection and obvious anaphylaxis were not present. One patient was taking liver extract, but the others were not. Of the 113 patients examined for fever or leukocytosis, 25.7 per cent had a temperature of at least 99 F or a leukocyte count of more than 10,000 cells.

*Spinal Fluid*—The spinal fluid was examined in 40 cases included in this study. In 3 of these the spinal fluid was normal. In 3 others an abnormality was not recorded, but no mention was made of the protein content. One patient was definitely syphilitic, and the values will not be considered except for the sugar content. The total protein content varied from 35 to 120 mg per hundred cubic centimeters, being above 50 mg in 22 cases and above 60 mg in 15 cases. Globulin was noted in the fluid in 33 cases, there being more than a slightest possible trace in 18 cases. One specimen was bloody and contained 286 white cells. In 1 other specimen there were 9 white cells. In all other specimens the white cell content was well within the normal limit. The colloidal gold curve was normal in all cases in which it was recorded, except that in case 10,451, that of the patient with the Charcot joints, it was 3444310000 and in case 8,428 it was 0123210000. The spinal fluid and blood were obtained simultaneously in 22 cases. The sugar content of the spinal fluid varied from 80 to 150 mg per hundred cubic centimeters, with an average of 99.5 mg, and its ratio to the sugar content of the blood varied from 34.8 to 85.7 per cent, with an average of 54.5 per cent. Rieger and Solomon (1916) reported the sugar content of the spinal fluid of 175 persons. They observed a range from 50 to 90 mg, with an average of 70 mg, except for the extremes noted in persons with diabetes and inflammatory conditions. Six diabetic persons yielded values ranging from 134 to 256 mg, but that was in the era before the use of insulin. Wahl (1931) reported simultaneous values of the blood and spinal fluid sugar for 5 patients. The ratio of

sugar in the spinal fluid to that in the blood was 75 per cent, being higher in the uncontrolled cases, and Steinitz' (1931) results were rather similar. My results show that the ratio for those patients with a sugar content of the blood of 200 mg or more was less than the average for the whole group. The spinal fluid in the cases reported on by Major (1924), Angle (1928) and Root and Rogers (1930) contained more than the normal amount of protein. Furthermore, in Angle's case there were 30 cells per cubic millimeter. In the case of diabetic tabes reported by Bostock (1926) there were also many cells and other abnormal findings in the spinal fluid, but the patient may also have had syphilis. In the case reported by Wright (1931) there were an increased globulin content and a colloidal gold curve of 1123210000.

*Special Features*—Pupillary Changes. Pupillary changes (including Argyll Robertson pupils) not due to syphilis have been reported in various conditions,<sup>8</sup> including neuritis and arteriosclerosis. Moore (1931) reported cases in which no known cause was noted. That diabetes is a cause of Argyll Robertson pupils was denied by Williamson (1907), Smith (1926) and Grafe (1927) but affirmed by Parker (1928). Adie (1931) and Merritt and Moore (1933) insisted that the true Argyll Robertson pupil is found only in syphilitic persons, and that those attributed to other conditions do not fulfil the requirements of Argyll Robertson. Pryce (1887) and Major (1924) each reported the case of a diabetic person with sluggish pupils, and Pitres (1902) noted the absence of the pupillary reflex in 1 of 32 diabetic persons. Laudenheimer (1896) reported the case of a diabetic patient with unequal pupils, and Ingegnieros (1905) mentioned the case of a diabetic patient with poorly defined Argyll Robertson pupils. I have encountered changes in the pupillary reflex in many diabetic patients for which there was no explanation except the diabetes. Most of my 23 patients with pupillary changes had definite abnormalities, although 1 patient had only inequality and irregularity of the pupils and 2 others had unequal pupils which reacted normally according to one observer but not according to another. In the other 20 cases there were indisputably abnormal reactions to light and distance or to light alone. A true Argyll Robertson pupil (fixed to light, reacting to distance, dilating only partially with mydriatics and in some cases contracted) was noted in 5 cases, and in 8 others there was sluggish response to light, with a normal response to distance. In 7 cases the pupils were fixed or sluggish to both light and distance. Irregular pupils were observed in 7 cases and unequal pupils in 5. Syphilis was not present in these

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<sup>8</sup> Tinel and Goldflam (1912) Mériel (1926) Thomas (1931) Wilson and Robertson (1932) Nielsen and Verity (1930) Feiling and Viner (1922) Ashby (1927) Voegtlin and Lake (1919) Woltman (1921) Price (1923)



cases according to the history, physical examination and Wassermann reaction of the blood. In 5 cases spinal puncture was carried out, and the spinal fluid did not show evidence of syphilis. In all the cases, of course, diabetes was proved, and in all but 1 there were other neurologic changes usually attributed to diabetes. One case was of the circulatory type, 13 of the degenerative and 8 of the neuritic. One was in the group with changes in the bladder. The youngest patient was 37 years old, but he was an astonishingly heavy drinker of whisky. The other 22 patients were 49 years of age or more, and all 23 had arteriosclerosis in only 2 of whom it was of slight degree. In resume, in 20 of these 23 cases there were definite abnormalities of the reflexes, with no apparent cause other than diabetes, arteriosclerosis and, in 1 case, alcoholism, although in 6 other cases the patient admitted some consumption of alcohol in the past.

**Involvement of the Optic Nerve.** Involvement of the optic nerve or retrobulbar neuritis has been described in connection with various conditions,<sup>9</sup> including peripheral neuritis. It has been mentioned in association with diabetes,<sup>10</sup> but other authors<sup>11</sup> have questioned or ignored this relationship. I have examined 2 diabetic patients with neuritis of the optic nerve with no obvious cause unless it was diabetes. One patient (case 9,312) with diabetes and arteriosclerosis had diabetic neuritis of the legs, which was quickly relieved. She then had some abscessed teeth removed. Several weeks later neuritis of the optic nerve developed. A boy (case 3,880) of 13 years had neuritis of the optic nerve without any apparent cause except the diabetes. In both these cases recovery occurred with no treatment other than the usual diabetic regimen.

**Paresis of the External Ocular Muscles.** Paralysis of the ocular muscles in persons with diabetes, according to Collier (1930), was described first by Ogle (1866). Lyon (1891) and Dieulafoy (1905) noted the frequency of this association, as did Collier, although Parker (1925) believed otherwise. Such paralysis may not always be apoplectic, as Collier stated. At times it resembles paralysis of the muscles of the legs associated with diabetes. The onset is not always abrupt, and recovery is rapid and complete in some cases. Furthermore, the

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9 Mayou (1926) Davis (1923, 1926) Harris (1914) Archer-Hall (1920, 1922) Smith (1929) White (1916) Stark (1921) Crane (1927) Mason (1922) Mahoney (1932) Aub

10 Tardieu (1862) Moore (1862) Raven (1887) Fraser and Bruce (1895, 1896) Moore (1921) Cohen (1923) Francis and Koenig (1926) Wagener (1929) Grafe (1927) Collier (1930) Dunphy (1930) Manes and Malbran (1931) O'Donoghue (1931)

11 Lépine (1909) Smith (1926) Parker (1925) Davis (1926) Paterson (1927)

condition of the eye is frequently associated with signs of diabetic neuropathy in other parts of the body, occurring in 3 of the 5 cases reported by Root (1922). Defective cranial nerves have been reported in other forms of neuritis,<sup>12</sup> and I have noted changes in the pupillary reflexes apparently due to diabetes. I report 1 case of diabetes with paralysis of the ocular muscles.

CASE 10,045—A 64 year old man with diabetes of seven and eight-tenths years' duration had paralysis of the muscles of the eye which developed over a period of from one to three days. Examination revealed moderate arteriosclerosis and paralysis of both superior rectus muscles and of the left external rectus muscle.

The involvement of the various muscles of the eye is difficult to explain on the basis of hemorrhage or thrombosis, and the onset of the condition was not abrupt. Furthermore, the patient had had pains in the legs, and the biceps reflexes were sluggish, although all the other reflexes were normal.

I report these cases only that they may be given consideration and not with the intention of classifying cases of this type in a definite way. The course in some of them resembles so much that in cases of diabetic neuritis and the association of arteriosclerosis and such neuritis occurs so often that I wonder if perhaps at times the ocular paralysis may not be of a nature similar to that of the neuritis.

Involvement of the Auditory Nerve. Neuritis of the eighth cranial nerve has been described. Davis (1916) reported the condition in syphilitic patients, MacKenzie (1916) reported it in a case of unknown origin, and Young (1932) reported the case of a patient with a polyneuritis with progressive tinnitus and nerve deafness. Wittmaack (1907), Heiman (1907) and Merrill (1911) described involvement of the eighth nerve in persons with diabetes, Merrill attributing it in his case to the toxemia of diabetes. I observed 1 patient (case 10,262) in whom deafness developed during the course of diabetic neuritis and whose hearing improved as the neuritis improved.

Facial Paralysis. Whether or not facial paralysis is ever of the nature of diabetic neuritis is difficult to say. That it is at times of an apoplectic nature is certain, but in the cases of peripheral origin it is not easy to say that it is not of the type seen in nondiabetic patients. Grégoire (1883) and Bernhardt (1899) noted the frequency of facial paralysis in diabetic patients, the former (according to Auché [1890]) attributing it to bulbar lesions. As mentioned before, facial paralysis occurs regularly in one type of polyneuritis, and it is not impossible that the condition occurring in diabetic patients is of the nature of diabetic neuritis. I included 2 cases of diabetes with facial paralysis.

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<sup>12</sup> Grimberg (1928) Taylor and McDonald (1932) Wilson and Robertson (1932) Dejerine (1914) Buzzard (1890) Aub

in this series In 1 (case 6,776) there was no other neuritic change In the second (case 5,361) painful diabetic neuritis developed, involving both legs, which was still present the last time I saw the patient In each case recovery of the facial movements was almost complete in about one year

**Paralysis of the Vocal Cord** I had 1 patient (case 9,429) who suffered from temporary paralysis of the superior laryngeal nerve associated with some tenderness of the thyroid region New and Childrey (1930) reported paralysis of this nerve associated with arteriosclerosis of the central nervous system, and my patient had moderate arteriosclerosis and signs of degenerative neuropathy of the legs The neuritis in this case may have been the result of thyroiditis of unknown origin and may have had no connection with the diabetes

**Abdominal Symptoms** The resemblance between tabes and diabetic neuritis has been commented on often, but usually with the reservation that Argyll Robertson pupils, Charcot joints, gastric crises and disturbances in the bladder do not result from diabetes I have already described the pupillary changes and the presence of Charcot joints in 1 case, and now I shall discuss the other two conditions

CASE 4,127—A 65 year old woman with diabetes of seven and nine-tenths years' duration was admitted to the hospital on account of nausea and abdominal pain The symptoms, of four days' duration, were severe but occurred only at night and were relieved by walking The examination revealed nothing abnormal except arteriosclerosis and diabetes Roentgen examination disclosed no abnormality A thorough search for diaphragmatic hernia gave negative results After a week at the hospital, with symptomatic and diabetic treatment, the nausea stopped, and the pain diminished considerably In this case the nocturnal occurrence of symptoms relieved by walking and recovery with the usual diabetic and symptomatic treatment suggested the possibility of diabetic neuritis

CASE 10,559—A 63 year old woman was admitted to the hospital with uncontrolled diabetes and pain in the leg associated with sluggish knee jerks and absence of ankle jerks Regulation of the diabetes relieved the pain at once Four months later the patient was readmitted with more definite neuritis in the leg This improved with treatment but recurred and persisted and became more widespread Four months after the second visit she was admitted again During the three months prior to admission, in addition to the obvious neuritis, the patient had had abdominal symptoms, beginning as a band of pain on the left side of the lower portion of the chest and the upper portion of the abdomen and after three weeks involving the right side also The pain was always worse at night After two months, the patient began to vomit, and this continued to the time she was admitted to the hospital As a result of the pain, vomiting and small intake of food, the patient was very thin, weak and a "nervous wreck" Her neurosis was exceptionally severe, but it was interspersed with occasional days of dilapidated cheerfulness Roentgen examination did not reveal pathologic changes except a gallstone With symptomatic treatment the patient improved somewhat, but progress was so slow that operation for the gallstone was performed The stone was reposing in an otherwise normal gallbladder, and no other abdominal abnor-

malady was disclosed. The vomiting, which had subsided just before the operation, recurred, and there was no amelioration of symptoms other than would be expected from the supportive treatment. The psychic disturbance was so great that the family acceded to the patient's request to take her home. During the next six months, with diabetic treatment, the nausea and vomiting stopped, and the neuritis in the legs improved.

This patient had definite diabetic neuritis and vague abdominal symptoms of insidious onset, similar to those of the usual neuritis. It is known that neuritis causes paresis of the skeletal muscles and that the psychic state of the patient varies in direct relationship to the neuritic symptoms. This patient had gastric atonia, and the gastric symptoms were better when she was less depressed. When depressed she would vomit almost as soon as the fluid intake by mouth amounted to from 16 to 24 ounces (472 to 708 cc), but not when she was cheerful.

In 2 more of the cases of neuritis abdominal symptoms were present, the condition in 1 (case 11,113) suggesting carcinoma of the cecum or the ascending colon. The patient may have had carcinoma, but the roentgen and physical examinations gave negative results. Pain was worse at night, and it extended into the leg and was associated with muscular paresis. Pryce (1919) reported a case of neuritis of the leg in which subsequently the condition seemed to be due to a probable carcinoma that was not discovered on the first examination. Time may prove that the condition in my case was similar, but I have been unable to trace the patient, even though her son is a physician. In case 9,009 the condition was tentatively diagnosed as ureteral colic. Pain began in the posterior portion of the left flank and had gradually extended around to the groin and testicle at the time the patient was admitted to the hospital. The pain was excruciating, in spite of injections of morphine. Gradually, the pain extended into the left leg and within a few days had reached the foot, disappearing above as it spread below. The tenderness moved with the pain from the region of the kidney to the leg, and muscular paresis and hyperesthesia of the leg appeared. The knee jerk, at first only sluggish, disappeared completely, to return in three months as the neuritis improved. Roentgen and urologic examinations did not disclose evidence of genito-urinary disease, and the subsequent course of the condition showed that it was definitely neuritis.

Other abdominal symptoms, such as those reported by Fiske (1925) and those occurring in diabetic acidosis, are not considered here.

**Disturbances in the Bladder** I am sure that disturbances in the bladder similar to those noted in syphilitic patients do occur in non-syphilitic persons with diabetes. Such changes are observed often in cases of tumor of the spinal cord and combined symptom disease, and such involvement has been reported with alcoholic neuritis by Boxwell (1914) and Campbell (1924), with lead poisoning by Campbell (1924) and Caulk and Greditzer (1916, 1917), with polyneuritis by Holmes (1917), Harris (1923) and Campbell (1924) and with diphtheritic neu-

itis by Kennedy (1933) Thus, it is hardly surprising that one occasionally sees such a condition in diabetic patients Le Biet (1852) was quoted by Marchal de Calvi (1864) as having reported the case of a diabetic person with slight disturbance in the bladder, but he did not disclose the nature of the disturbance Bonardi (1897) reported the case of a diabetic patient, 72 years old, with loss of sphincter control Von Noorden and Isaac (1927) referred to urinary urgency, especially at night, not apparently due to the polyuria shown by diabetic persons McKittick and Root (1929) reported neurogenic disturbances in the bladder in patients with diabetes In the case of *tabes diabetica* reported by Angle (1928) symptoms in the bladder were relieved by the diabetic treatment, but there was also an enlarged prostate, and it seems probable that symptoms in the bladder were due to swelling of an already enlarged prostate, irritated by the uncontrolled diabetes

I have examined 12 diabetic patients with urinary retention or incontinence or both, apparently due to diabetic neuropathy None of the patients was syphilitic, nor did I find evidence of any nervous disease except diabetic neuropathy The symptoms were not dependent directly on uncontrolled diabetes in the ordinary sense of the word or on a basically urologic factor Seven of the patients had urinary retention, and the other 5 had incontinence suggestive of paresis of the sphincter The first 7 cases are being reported in the *ARCHIVES OF INTERNAL MEDICINE* In 7 cases the symptoms in the bladder began during the course of diabetic neuritis, and in 2 others there were signs indicative of the degenerative diabetic neuropathy Arteriosclerosis was present in 11 cases and was not mentioned in the twelfth The youngest patient was 42 years old

CASE 5,494—A 47 year old man noted involuntary urination at night at the onset of the diabetes Five years later he noted paresthesia of the legs and, subsequently, pains in the legs Two years later the bladder was observed to be distended (residual urine, 360 cc) Examination revealed moderate arteriosclerosis, normal pupils and cranial nerves, sluggish knee jerks and ankle jerks, weakness, atrophy and fibrillary twitchings of the muscles of the legs and less of the arms, and variable cutaneous sensitivity, with areas of both hypo-esthesia and hyperesthesia The Wassermann reaction of the blood was negative, and the spinal fluid was normal, except for the slightest possible trace of globulin A history of alcoholism was not obtained Urologic examination revealed slight irregularity of the prostate, which was insufficient to cause obstruction Trabeculation of the bladder was moderate

The patient died seven months after examination of gas bacillus infection following an appendectomy

CASE 9,759—A 62 year old woman with diabetes of five and one-half years' duration and moderate arteriosclerosis was suffering from progressive diabetic neuritis of rather recent onset During the evolution of the neuritis, she noted difficulty in retaining the urine There was no burning or urgency but merely

difficulty in retaining the urine after a certain length of time. Examination did not disclose distention of the bladder or infection of the urinary tract. The knee jerks and ankle jerks, which had been normal a few months previously, became sluggish as the neuritis in the legs progressed. Considerable psychic depression also supervened, such as is often seen in cases of diabetic neuropathy. Although there was achlorhydria, there was no other evidence of combined system disease. There was no history of alcoholism or syphilis.

Although there is something horribly similar between syphilis of the nervous system and diabetic neuritis, there is also something pleasantly different. In the latter condition markedly incapacitating symptoms seldom occur, and this period of incapacity usually passes within a few months. Nor do the changes in diabetes usually progress or persist to the degree seen in syphilis. A diabetic person rarely experiences individually the many infirmities which one not infrequently sees in a tabetic patient.

**Psychic Symptoms** The occurrence of psychoses with nonalcoholic neuritis and with plumbism was noted by Korsakow (1890), Harris (1923) and Aub. Cerebral symptoms, probably apoplectic, were described in diabetic patients by Marchal de Calvi (1864) and Desbonnets (1899), and Miles and Root (1922) and Dashiell (1930) studied the mental efficiency of diabetic persons. Depression, hypochondriasis, delirium, suicidal tendency, hallucination and ideas of persecution have been described.<sup>13</sup> Many times these symptoms were not produced by painful neuritis. Alcoholism was present in some cases but not in all. Masson (1923) listed diabetic toxin, arteriosclerosis, menopause and heredity as etiologic factors. The prognosis supposedly varies directly with the control of the diabetes. Diabetic pseudoparesis was mentioned by Laudenheimer (1896), Ingegnieros (1905), Bostock (1926) and Williams (1932). Diabetic treatment proved efficacious in the cases of the first three authors.

The psychic state usually encountered in patients with diabetic neuritis is evidenced by inordinate depression and emotional instability. Nervousness is often extreme, and the patient will neither rest nor be comforted. At times the symptoms are out of proportion to the apparent severity of the neuritis. Of 105 patients with neuritis, 52.4 per cent showed a sufficient degree of depression or nervousness to mark them as abnormal, and 14.3 per cent showed a marked degree of it. One patient (case 9,680) was totally irresponsible and was confined in a psychopathic hospital with a diagnosis of involutional psychosis. She also had neuritis of the external popliteal nerve. Another patient (case

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13 Legrand du Saulle (1877, 1884) Lepine (1909) von Liebe (1889) Cohn (1892) Laudenheimer (1896, 1898) Madigan (1883) Mendel (1889) Bond (1896) Halberstadt and Arsimoles (1911) Sittig (1912) Singer and Clark (1917) Pike (1921) Reiter (1926)

6,659) became extremely irritable and completely unmanageable and suffered at home from brainstorms, so that his mother was forced to take him to a sanatorium for safe-keeping, but on the trip his psychic and neuritic symptoms improved so much during a stop at a "hot springs" resort that confinement in the institution became unnecessary. With continued physical therapy, especially massage, the patient recovered completely.

Not only do psychic symptoms occur in persons with neuritis, but neuritis is prone to affect nervous patients with diabetes. About 60 per cent of the first 100 neuritic patients examined had a nervous temperament. This may be due to the susceptibility to injury of a sensitive nervous system or to the more frequent detection of neuritis in complaining than in phlegmatic persons. Twice following emotional shocks one patient (case 9,340) had an exacerbation of symptoms. Such nervousness makes difficult an accurate estimation of cutaneous sensitivity and improvement in the neuritis.

*Differentiation Between Poliomyelitis and Neuritis*—Included in this series are 2 cases which puzzled my associates and me because we could not decide whether the condition resulted from the effects of anterior poliomyelitis or from neuritis. To differentiate between these conditions is not always easy, as Dejerine (1914), Joughin (1915) and Harris (1923) pointed out. Involvement of the cells of the anterior horn of the spinal cord has been recorded in various forms of neuritis: in experimental beriberi by Eijkman (1897), in lead poisoning by Hyslop and Kraus (1923) and in diabetes by various authors.<sup>14</sup> In some cases of diabetic neuritis there is rather sudden paralysis of isolated muscles or groups of muscles without other signs of neuritis. The 2 cases included in this study may fall into that group or there may have been true poliomyelitis. I dare say that the condition in both cases would have been unquestionably accepted as neuritis if it had occurred in elderly patients. In the following case the condition was diagnosed as poliomyelitis by the orthopedic consultant and as probable neuritis by the neurologist.

CASE 9,230—A boy of 18 years, with diabetes of five weeks' duration, was unconscious when admitted to a hospital, where he was treated for diabetic coma. When he regained consciousness he complained of pains in various places and weakness of various muscles. Shortly afterward he was transferred to the New England Deaconess Hospital. I observed that all the muscles were weak and small. There was wrist drop, and the triceps muscles were very weak. The muscular paresis involved the legs but to a slightly less extent than the arms. There was absence of the triceps reflexes and of the right knee jerk. The left

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14 Leichtentritt (1893) Nonne (1896) Bonardi (1897) Marinesco (1901) Findlay (1902) Bramwell (1907)

knee jerk was sluggish. All other tendon jerks were normal. There was considerable tenderness of both the muscles and the nerves, especially of the upper radial and the right femoral muscle and nerves. The left wrist was swollen, and the patient said that his feet had been swollen just after he recovered from coma. He also stated that his right thumb had been numb, possibly before the onset of coma as well as after. Improvement began in about five weeks and was practically complete in nine months. Fifteen months after the onset the patient had no symptoms and felt as strong as ever, but atrophy, especially of the muscles of the shoulder and the left triceps muscle, was still present, and the left radial tendon jerk and both triceps reflexes were slightly weak.

In 1 other case (case 10,405) the patient first noted paralysis after he recovered from diabetic coma. This patient had merely a left foot drop, which disappeared in six months with the usual treatment for diabetes and neuritis.

*Pathology*—We have no pathologic data on these cases. Auché (1890) described myelin degeneration and other changes in the nerves of a young diabetic patient with neuritis, and Wittmaack (1907) described degeneration of the eighth cranial nerve of a diabetic girl 10 years old. It is possible that the pathologic changes in these cases with neuritis were similar to those described by other authors in the cases with associated degenerative neuropathy.

*Etiology*—The etiology of the neurologic changes in diabetes has been variously attributed, at least partially, to the excess of sugar,<sup>15</sup> cachexia,<sup>16</sup> venous congestion of the abdominal organs (Rosenstein 1882), incomplete combustion of the organic acids (Charrin and Guignard, 1882), vascular disease,<sup>17</sup> dehydration (Auché, 1890; Dieulafoy, 1884), an unknown toxin due to the diabetic condition,<sup>18</sup> acetonemia<sup>19</sup> and deficiency disease (Harris, 1922). Auché studied the effect of various solutions of sugar on nerves and concluded that sugar alone was not the cause of these changes, although in concentrated solution it caused injury. Eichhorst (1892) put nerves in solutions of dextrin, acetone, beta-oxybutyric acid and physiologic solution of sodium chloride and did not note distinguishing changes. Pitres and

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15 Marchal de Calvi (1864) Christ-Bucli (1873) Worms (1880) Drasche (1882) Barth (1883) Dreyfous (1883) Florain (1885) von Hossln (1886)

16 Althaus (1890) Raymond and Oulmont (1881) Bernard and Feré (1882) Pryce (1893) Woltman and Wilder (1929)

17 Bouchard (1882) Pryce (1893) Woltman and Wilder (1929) Root and Rogers (1930) Labbé (1931)

18 Fraser and Bruce (1896) Pryce (1887) Eichhorst (1889) Auché (1890) Merrill (1911) Pike (1921) Williamson (1907) Sergent and Kaufmann (1925) Root and Rogers (1930)

19 Auché (1890) von Liebe (1889) Cohn (1892) Laudenhimer (1898) Lépine (1909) Sittig (1912)



Auche (1901) were unable to produce neuritis by the injection of sugar, but Wight (1931) said that Grube reported marked neuritis after such an injection

In my group of cases with neuritis were some in which neuritis evidently developed, at least partially, from factors not connected directly with the diabetes. I consider these factors as accessory or precipitating causes, because I believe that the diabetes first makes the patient abnormally susceptible to such factors

**Sex and Age** Sixty-nine patients (57.5 per cent) were female and 51 (42.5 per cent) were male. The age at the onset of the neuritis varied from 13 (in case 3,880, with optic neuritis) to 76 years (case 990), the average age being 54.7 years. Only 12.5 per cent of the patients were less than 40 years, and only 5.1 per cent were less than 30 years, whereas 40 per cent of all persons with diabetes have the disease before the age of 40 (Root, 1934). Two patients were less than 20 years old, 1 (case 3,880) had neuritis of the optic nerve and the other (case 9,230) may have had poliomyelitis and not neuritis. This low incidence in young persons may be associated not only with the low incidence of vascular disease but also with the incomplete development of the myelin sheaths, since Moore and his co-workers (1927) noted in their experiments that neuritis did not appear in young rats until the time when the myelin should be fully laid down. Careful study of all cases of neuritis in young persons with diabetes should be worthwhile. Maiton (1929) observed that both diabetic and nondiabetic persons showed decreased nerve-muscle irritability in proportion as the age increased.

**Duration, Severity and Control of the Diabetes** The duration of diabetes at the onset of the neuritis varied markedly. Four patients had neuritic symptoms before the apparent onset of the diabetes, and in 7 others there was a simultaneous onset of the two conditions. Buzzard (1890) reported a case in which thirst and polyuria supervened during the course of neuritis. In 1 of my cases the diabetes had existed for twenty-nine years before the neuritis was noted. The average duration of the diabetes prior to the onset of neuritis in the 120 cases was five and nine-tenths years, and in 28 cases diabetes had been present for only one year or less. In 42.2 per cent of the cases the diabetes was mild,<sup>20</sup> in 43.6 per cent, moderate, and in 15.9 per cent, severe. In 35.9 per cent of the cases glycosuria was not present (based on tests carried

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<sup>20</sup> The mild cases were those in which the usual daily dose of insulin was from 0 to 9 units, the moderate cases, those in which the usual daily dose of insulin was from 10 to 29 units and the severe cases, those in which the usual daily dose of insulin was 30 units or more. All the patients were on an adequate diet with the diabetes controlled.

out in the hospital or reported by patients) prior to the onset of the neuritis, and in 11.7 per cent more there was only slight glycosuria a total of 47.6 per cent in which the diabetes was at least fairly well controlled. Furthermore, in 50 per cent of the cases in which I could judge the effect of regulation of the diabetes, there was no apparent effect on the neuritis, but it must be stated that controls were not used. A slight benefit resulted in 21.7 per cent. In some cases control of the diabetes did not cause apparent benefit, even over a period of months. It is difficult to believe that hyperglycemia alone causes this neuritis although Marton (1929) noted decreased nerve-muscle irritability in proportion as the sugar content of the blood rose and the duration of the diabetes increased. The early experiments, with the exception of Grube's, bore out this statement. Kraus (1920) expressed the opinion that the severity of the diabetes was of importance but not the duration. Harris (1922) expressed the opinion that neither ketones nor sugar was the cause. Herschmann (1932) reported neuritis in cases of latent diabetes similar to that in my case 10,582. There must be some factor as yet unknown, that gives rise to diabetic neuritis. The fact that one observes neuritis so often in diabetic patients is fairly good evidence that diabetes in some way causes neuritic changes.

**Cholesteremia.** The fact that the lipid myelin sheaths of the nerves bear the brunt of the attack suggests that the disturbed fat metabolism of diabetic persons may be connected with the neuritis. Certainly frank acidosis was not an important factor in this group of cases. The cholesterol content of the blood was determined in 44 cases, but unfortunately one cannot always make an examination at or before the beginning of the neuritis. When carried out subsequently it may give an erroneous idea because of the upset in the diabetes that is likely to be caused by severe neuritis or it may be a false value caused by the previous institution of diabetic treatment. The values in my cases ranged from 120 to 445 mg., with an average of 233.8 mg. the normal being not more than 230 mg. Values above 230 mg. were obtained for 52.3 per cent of the patients examined, but 1 of the patients had nephritis with edema. In studying the relationship between neuritis and fat metabolism I have collected diabetic nerves for analysis in the laboratory of Dr William R. Bloor. The lipid constituents show definite abnormalities which are being reported in the *ARCHIVES OF INTERNAL MEDICINE*.

**Dehydration.** The upset in water balance, with resulting dehydration occurring in untreated diabetic persons might be considered to exert some influence but in 84.8 per cent of the cases there was no obvious dehydration. One patient (case 10,216) obtained no relief from the pains when saline solution was administered intravenously at the beginning of diabetic treatment. One frequently observes diabetic patients

with marked dehydration and no neuritic symptoms, and in 1 such patient neuritis developed after dehydration was entirely relieved

**Arteriosclerosis** Arteriosclerosis is associated with many neurologic conditions<sup>21</sup> and seems to play a causative rôle. It involves the peripheral<sup>22</sup> as well as the central nervous system. In diabetic persons the legs are markedly affected by arteriosclerosis but, as Morrison and Bogan (1929) pointed out, seldom when the patient is less than 40 years of age. If one assumes that arteriosclerosis is a factor in the production of diabetic neuropathy, the observations of Morrison and Bogan are compatible with mine, that neuritis and degenerative lesions usually affect the legs and occur rarely in diabetic persons less than 40 years old. As early as 1893 Pryce suggested extensive vascular disease as one of the causes of diabetic neuritis. Rimbaud (1909) entertained a similar idea, and Woltman and Wilder (1929) expressed the opinion that arteriosclerosis is the most important cause. Many times one notes in the literature the association of arteriosclerosis and this neuropathy. Marinesco (1901) noted thickening of the walls of the intraneural vessels. The 3 diabetic patients with paralysis whose cases were reported by Root (1922) all had arteriosclerosis.

Among the 120 cases in this group, arteriosclerosis was present in all except 9 (7.5 per cent), although it was only slight in 7 cases. Disease of the coronary vessels was present in 20 per cent, and in 30.8 per cent there was evidence of angina pectoris, apoplexy or a circulatory condition of the feet requiring surgical intervention. Of the 9 cases without arteriosclerosis, there was no pulsation in the dorsalis pedis artery in 2, and in 1 of these the oscillometer needle showed diminished excursion at the level of the left calf. One patient was a man of 39 years, who had had diabetes for two years. The fourth was a woman of 50 years with diabetes, and she may have had arteriosclerosis which was not disclosed by palpation of the radial artery. The fifth and sixth cases were the 2 discussed as possible cases of poliomyelitis. The seventh patient was the boy with neuritis of the optic nerve. The eighth was a man of 35 years with diabetes of twelve years' duration and some obvious but undiagnosed infection that may possibly have been similar to the infectious neuritis recently described by Taylor and McDonald (1932). Furthermore, there was evidence of some impairment of the circulation in the legs. The last patient (case 7,538) was a woman 21 years old who had had diabetes for five years. Neuritic pain was promptly relieved by diabetic treatment, but sluggish activity of the

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21 Woltman (1921) Price (1929) Wright (1924) Critchley (1931) Bing (1932)

22 Schlessinger (1895) Franceschi (1903) Woltman (1921) Price (1923) Priestley (1931) Alpers and Wolman (1931)

reflexes persisted. The youth of 18 years (case 5,932) in the hyperglycemic group, in whom sluggish reflexes developed subsequently, was suffering from active pulmonary tuberculosis as well as from uncontrolled diabetes.

It is not sufficient to examine only one artery to determine the presence of sclerosis. At times the sclerosis is much more advanced in one site than in another. In case 10,100 there was only slight detectable sclerosis in the radial arteries, yet roentgenograms showed sclerosis of 4 plus degree in the legs. Similarly, in case 4,458 there was only slight sclerosis in the optic fundi, yet sclerosis of 4 plus degree was present in the legs. Even in the same artery, the sclerosis varies in degree at different places. A cursory examination is sometimes misleading, but, even considering this, I noted moderate or advanced arteriosclerosis in 86.7 per cent of the cases. Evidence of impaired circulation in the legs, as judged by the methods recommended by McKittrick and Root (1929), was present at least to a slight extent in 65.8 per cent of the cases in which a test was made.

Of the 120 cases there were 5 in which there was no evidence of vascular disease either by signs of arteriosclerosis or by defective circulation in the legs. The absence of detectable vascular disease in these 5 cases indicates either that arteriosclerosis is not the only cause of diabetic neuritis or that the condition in these cases was not diabetic neuritis. Other evidence against the theory that arteriosclerosis is the chief cause of diabetic neuritis is found in the relative rarity of neuritis in elderly nondiabetic patients with arteriosclerosis. In 10 cases in patients 70 years or more of age there were no neuritic symptoms and the knee jerks were normal. The ankle jerks were normal in 9 cases. In the tenth case the right ankle jerk was sluggish and the left absent. Sensation to pinprick was normal in the 2 cases tested. These findings are compromised by the fact that I have not made studies on a large group of cases, but certainly they are at variance with my findings in diabetic patients of similar age or with a similar degree of sclerosis. Even among diabetic patients sclerosis does not invariably produce manifestations of neuritis. Even when the sclerosis is so advanced that the feet and lower portion of the legs are dusky red, there may be no evidence of neuritis. In 5 such cases recently observed the only evidence of neuritis was sluggishness of the ankle jerks in 1 case. Deficient circulation probably plays its part in addition to the sclerosis. It seems to cause hypesthesia, which was well shown in case 4,319. The patient had hyperesthesia of the leg from the hip downward to the middle of the lower part of the leg, where there was a gradual transition to the hypesthesia existing below this level, and this hypesthesia coincided with the dusky area caused by impaired circulation. But that

hypesthesia is not due solely to the vascular disease is indicated by the experience of surgeons who have noted insensitivity to a much greater extent in patients with diabetic gangrene than in nondiabetic patients.

The fact that the symptoms appear rather suddenly and that the signs as well as the symptoms improve or even disappear is no proof that arteriosclerosis is not a cause. The optic neuritis in the case reported by Alpers and Wolman (1931) disappeared clinically, although the sclerosis of the vessels had advanced so far by the time of death that the optic nerves were cut almost in two by the compression. Furthermore, it is known that the signs of apoplexy disappear and that retinal hemorrhages are absorbed spontaneously (Genet 1927). An abrupt onset of pain, such as occurred in case 9,078, may be explained by a hemorrhage involving the nervous system. The indefinite and widespread nature of the neuropathy and the patchy distribution of the pathologic changes described by Woltman and Wilder (1929) may be explained by such a widespread and patchy distribution of arteriosclerosis as one sees in diabetic patients. A condition of repeated multiple minute hemorrhages, such as those in a case reported by Raeder (1921) in conjunction with pressure from thickened arteries and the impairment of nutrition of the nerve tissue, may explain many of the phenomena seen in cases of diabetic neuropathy. René le Fort (1916) reported a case of neuritis, especially of the sympathetic system, in the leg caused by hemorrhage from a contusion. Ischemic neuritis has been described by Chavany (1931), and Priestley (1931) attributed to ischemia the degeneration he noted in cases of arteriosclerotic gangrene. It seems unlikely that ischemia or Volkmann's (1881) contracture plays any role in the production of diabetic neuritis.

One feature not easily explained is the nocturnal occurrence of the neuritic symptoms, which is true in cases of involvement of the leg, the arm and the abdomen. It occurs in young diabetic persons with symptoms of hyperglycemia and no evident vascular disease, as well as in older, arteriosclerotic patients. It occurs in phlegmatic as well as in nervous persons. If one attributes it to ischemia, how is one to reconcile it with Lewis' (1932) contention that the pain of ischemia arises from a working muscle, especially since diabetic patients obtain relief by pacing the floor? Furthermore, it must be attributed to arterial rather than to venous incompetency, for the latter condition is apt to be improved when the patient is prone, and yet many young diabetic patients without demonstrable arterial disease suffer from pain of this character. The explanation that at night all is quiet and one has the opportunity to humor one's ills hardly seems acceptable because of the difference in temperament in various patients with the symptom. Furthermore, walking around a room at night is not a well recognized

sedative Nor does it seem reasonable that, were the pain based on an emotional state, so many patients would have such severe pain at night and not notice it during the day

**Anemia** Another aspect of ischemia is furnished by anemic persons Van Bogaert (1927) reported a case of splenic anemia with peripheral neuritis In the only case of severe secondary anemia in this series (case 11,253) there were also advanced arteriosclerosis and chronic infection of the leg Pernicious anemia is a different matter My cases had something in common with cases of pernicious anemia (Smithburn and Zerfas, 1931), but in the case of multiple neuritis with pernicious anemia reported by Robertson and Gowen (1930) spasticity and increased tendon reflexes were present, neither of which has been present in any of my cases of neuritis Of course, combined system disease is associated with marked nervous changes and I had 4 cases of pernicious anemia in this series In each there was absence or sluggishness of tendon reflexes, and there were clinical features which suggested that diabetes played a part also in the production of the condition The fact that of 46 of these cases tested achlorhydria was present in only 30.4 per cent and the average amount of free hydrochloric acid was 33.9 degrees is good evidence that the presence of pernicious anemia is not essential for the development of diabetic neuritis As a matter of fact, the incidence of achlorhydria in unselected cases of diabetes is 39 per cent (Rabinowitch, Fowler and Watson, 1931)

**Dietary Deficiency** Root and Rogers (1930) suggested that diabetic neuritis might be due to food deficiency, such as occurs in cases of beriberi This idea has been indirectly or directly expressed by many authors for many years Marchal de Calvi (1864) noted that a not too great restriction of the diabetic diet was more likely to give relief from sciatica than keeping the patient aglycosuric, and Althaus (1890) confirmed this Bouchard (1884), Raven (1887), Woltman and Wilder (1929) and Schmidt (1930) noted return of the knee jerks in diabetic persons regaining proper nutrition and health Angle (1928) reported improvement in a case of diabetic tabes in which the carbohydrate content of the diet was increased, and this occurred in my case 8,166 Nutritional polyneuritis, such as that reported by McCollum and Kennedy (1916), is well recognized as being due to a deficiency of vitamin B and is cured rapidly by the administration of vitamin B There are some points of resemblance between it and diabetic neuritis For example, its effect (Voegtlin and Lake, 1919) on the pupillary reactions, its tendency to affect chiefly the hindlegs of cats, its tendency to cause slight changes in the cord and more marked changes in the myelin sheaths of the nerves, especially that of the sciatic nerve, are similar to the changes wrought by diabetes Then there is neuritis

attributed to nonspecific food deficiency (Gram, 1924, Shattuck, 1928, Wechsler, 1930) Wechsler suggested that this might be the cause of diabetic neuritis. It is known that occasionally diabetes is associated with some dietary deficiency disease (Wohl, 1926, Bitzer, 1931), and it is only reasonable to suppose that it occurs in other diabetic persons with a deficiency not severe enough to cause recognizable symptoms. Such a deficiency might be a cause of the neuritis. The course under treatment corresponds to that noted by Sugiura (1918) in birds with nutritional polyneuritis, although recovery is not usually so prompt in cases of diabetes, certainly not so prompt as that reported in cases of nutritional neuritis by Voegtlin and Lake (1919) and McCollum and Kennedy (1916). One of my patients obtained relief from neuritis in the leg within two weeks after she began taking yeast but, while taking the yeast, there developed neuritis of the optic nerve of no known cause unless it was diabetes. Against the hypothesis of a nutritional cause is the fact that of 63 of the patients questioned about any previous abnormality in the diet only 1 admitted a definite deficiency. The patient ate very little meat, cheese and eggs, but, on the other hand, she drank a great deal of milk daily. Two other patients ate only a little meat, and 1 ate very few green vegetables. The diabetic diet is fairly rich in vitamin foods: meat, green vegetables, butter, cream, cheese and fruit. And patients on such a diet do have neuritis. Furthermore, many of the patients improve or recover without any change in diet. Still more evidence is derived from the fact that the addition of yeast, cod liver oil or liver in some form has not hastened recovery, as compared with recovery in patients not so treated. It is conceivable that the deficiency lies in the absorption or utilization rather than in the consumption. Against that are the facts that patients recover without any dietary change and that children, who have the severest and least well controlled diabetes, seldom have neuritis. An answer to the latter may lie in the supposition that the neuritis depends partly on arteriosclerosis which is rarely severe in children. I might state that I do not call a diabetic patient a child simply because diabetes developed in his childhood. If the patient lives he will eventually become an adult and will become subject to the factors operating in adults.

**Lipase.** One highly hypothetical etiologic factor was suggested by the work of Brickner (1931), who found myelinolytic activity in the blood serum of patients with multiple sclerosis. Cherry and Crandall (1932) and Weil and Crandall (1932) investigated such lipolytic activity in the blood after pancreatic and after hepatic injury. The latter authors concluded that in experimental damage to the liver a neurotoxic agent is present in the blood serum. In 39 of 100 patients with diabetes Meyer (1931) noted definite laboratory evidence of hepatic dysfunction, which

occurred most frequently in the older patients in whom the diabetes had remained uncontrolled for a long time. Furthermore, he observed that the modern treatment for diabetes aids in improving hepatic function. These observations present an interesting possibility yet to be investigated.

*Accessory Causes*—Insulin Caravati (1933) reported a case of neuritis caused by insulin with numbness, tingling and pain in the legs occurring only with the use of insulin, to which the patient was sensitive. It at least gives one food for thought. I have observed patients in whom neuritis developed in the hospital immediately after the diabetes had become controlled. It was puzzling, and the insulin administered was a conceivable cause. It is well recognized that insulin causes local and general cutaneous anaphylaxis, and at times its administration is followed by hemorrhage.<sup>23</sup> Wohlwill (1928) observed cerebral pathologic changes which he attributed to hypoglycemia caused by insulin. Tzanck and Weismann-Netter (1929), Gordon (1932), Wilson and Hadden (1932) and Young (1932) described anaphylactic neuritis, and Campbell and Allison (1932) described cases of neuritis and urticaria. Insulin might act in such a way. The urticaria produced by insulin usually ceases within a few weeks, even when the same dosage of insulin is continued, and neuritis at times improves in a similar length of time. In 31.6 per cent of 98 cases in which I know whether or not insulin was being used at the time the neuritis began, insulin was being taken. In 2 of these cases (cases 9,230 and 10,405) neuritis was noted when the patient recovered from coma, the first time that insulin had been administered. In 6 other cases (cases 5,390, 8,962, 9,338, 9,452, 9,746 and 10,407) neuritis developed while insulin was being administered in the hospital. One of the patients was thin and confined to bed, and another was thin and had been crossing his legs. It seems likely that the foot drop and toe drop in these 2 cases resulted from pressure, as described by Woltman (1929, 1930). One patient (case 9,452) became aglycosuric in the hospital, foot drop developed at the end of his stay, and he recovered from it within two weeks. I hesitate to attribute any of these cases to insulin, and yet I can offer no better explanation.

*Alcohol* Although 2 of the patients with ataxia said that they used alcohol to some extent, I did not find that alcohol was a factor of much importance in the series as a whole. I have a record of the admitted intake of alcohol in 97 cases, 79.4 per cent of the patients were total abstainers, and an additional 13.4 per cent said that they used it in only slight amounts.

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<sup>23</sup> Gudemann (1926) Henderson (1927) Neale (1928) Lawrence and Hollins (1928)



**Focal Infection** A focus of infection was present in 38.5 per cent of the 104 cases about which there is a record of the presence or absence of the usual foci, but in some of these the focus had been removed some time previous to the onset of the neuritis. There seemed to be a definite association between the neuritis and the focus of infection in 3 cases (cases 8,112, 9,312 and 10,773). In 1 of these, treatment of an infection of the sinuses was followed by a rapid disappearance of the neuritis. In another, amelioration followed the extraction of an abscessed tooth. In the third case the neuritis flared up once after tonsillectomy and once after extraction for an abscessed dental formation. Whether there was a specific streptococcus present as in the case reported by Rosenow (1916), I cannot say. In case 4,319 the neuritis followed an attack of gallstones. Other sources of infection noted in this series were perinephritic abscess and pulmonary tuberculosis. The effect of the tuberculosis is problematic. Timel and Goldflam (1912), Tarchetti (1918), Harris (1922) and Levy-Valensi (1925) reported cases of neuritis in tuberculous patients, but Tarchetti noted that the condition in his 10 cases was due to aconite medication. It is worthy of note that in the cases of the hyperglycemic type the only 2 cases in which there was not prompt response to diabetic treatment the patient had tuberculosis and abscessed teeth, respectively. In the cases of the neuritic type 1 of the patients having only slight arteriosclerosis was tuberculous.

**General Infection** Wilson (1923) reported 2 cases of neuritis which he attributed to influenza. One of my patients (case 8,167) had neuritis associated with fever and symptoms which simulated influenza. He was 29 years old, had had diabetes for four years and had only slight arteriosclerosis. Another patient (case 10,265), a man 35 years old, had had diabetes for twelve years, and arteriosclerosis was not detectable. His neuritis was of the sensory type, with exquisite pain and hyperesthesia. It was associated with fever and leukocytosis of considerable degree. The 2 cases may be instances of the infectious type of neuritis previously mentioned, although facial paralysis was not present in either case. Syphilis was present in 3 of the 120 cases and had been present in 1 other case, with apparent recovery. In 2 of the 3 cases there was prompt response to diabetic treatment, and in all 4 cases there were features that suggested that diabetic neuritis was present in addition to the syphilitic process. It seemed improbable in any case and impossible in some that the neuritis resulted from the arsphenamine commonly used in the treatment of syphilis, although it has been known for many years that arsenic is a potential cause of neuropathy (Minor, 1889, Sézary and Chabanier, 1925).

**Toxic Causes** In no case did I note plumbism or any known toxic condition. Of course, it is not easy to remember to question each

patient about the use of depilatory cream or other products which are rarely toxic, and it is possible that I have overlooked cases such as those reported by Short (1931) and Mahoney (1932). Certainly I did not recognize cases of paralysis due to Jamaica ginger such as that reported by Harris (1930) and many others.

*Orthopedic and Mechanical Causes*—Various orthopedic or mechanical causes of neuritis have been reported,<sup>24</sup> and among my cases are some in which the condition was probably affected by such factors. Subdeltoid bursitis, sacro-iliac strain, pressure from crossing the legs or lying in bed and inactivity or excessive use of an extremity have contributed to the neuritis. Toe drop in thin patients has followed rest in bed or crossing the legs in a number of instances. Often the neuritis involved nerves other than the nerve affected by the orthopedic condition. Conditions resembling neuritis from a subdeltoid bursitis have had features suggesting that the process was in reality diabetic neuritis or at least was affected by the diabetes, and Sergent and Kaufmann (1925) stated that in all cases of circumflex neuritis diabetes should be suspected. Occasionally the mechanical cause seemed too slight to have produced neuritis unless the patient was susceptible to neuritis on account of preexisting diabetes.

CASE 22,576—A 45 year old man with diabetes of twelve years' duration complained of pain in the region of the shoulder joint and upper part of the arm and of difficulty in elevating the arm. The pain was much worse at night and disappeared when the patient paced the floor. There were moderate arteriosclerosis, tenderness along the course of the radial nerve and in the area of the subdeltoid muscle and normal reflexes. There was no paralysis or atrophy. The pain was similar to that experienced by patients with diabetic neuritis.

CASE 10,407—A 55 year old man with diabetes of ten months' duration, advanced arteriosclerosis and active pulmonary tuberculosis had worn rather tightly fitting round garters for a few days early in September. About a week later, while he was attending a lecture, he sat with his right leg crossed over the left. He noticed a beginning numbness in the toes of the right foot. He thereupon reversed the position, only to notice numbness in the left foot. Associated with this, as he ascertained a few minutes later when he returned to his room, was his inability to elevate the left great toe or to spread apart the toes, as he had done earlier that day. Within a few days, passive and active exercise of the affected muscles resulted in improvement.

*Miscellaneous Factors*—Occupation, fatigue and mental strain seem to have little or no effect on the causation of the neuritis, although neuritis did occasionally occur in patients at a time when they were under the strain of excessive work or responsibility. Since most of the patients lived in New England and were exposed to only one climate,

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<sup>24</sup> Guillain (1901) Rimbaud (1909) Breneman (1912) Babinski (1915) Woltman (1929, 1930) Ober (1930)

I have no data on the effect of climate, except that in a few cases the neuritis was worse in inclement weather. In some cases the neuritis began in midsummer and in others in the winter.

In summing up the etiologic data I may say that diabetic persons suffer from neuropathy of three types: (1) hyperglycemic, (2) degenerative and (3) neuritic. The first seems to be due to hyperglycemia or some closely associated condition, without regard to the presence or absence of vascular disease. The degenerative lesions seem to depend on an unknown diabetic factor and vascular disease. Although these lesions seem definitely associated with vascular disease, one must not forget that the arteriosclerosis and the neuropathy may be due to the same cause. The one may be merely an accompanying condition and may have no etiologic significance with respect to the other. Sluggish circulation in the lower part of the legs apparently leads to two symptoms, intermittent claudication and cutaneous hypesthesia, but the other symptoms noted in these cases seemed more likely to be due to arteriosclerosis. How diabetes causes neuritis, as opposed to degenerative neuropathy, is unknown. Vascular disease is usually, but not always, present. In some cases without such vascular disease infection seems to play a contributory rôle, and in all such cases a thorough examination for the secondary or precipitating cause should be made. Diabetic persons are subject to forces, such as pressure and alcohol, which produce neuritis in nondiabetic persons, but I believe that even in these cases the diabetes renders the patient more susceptible to the nondiabetic agent and modifies to some extent the type or severity of neuritis produced. Therefore, I caution my patients to avoid carefully such agents as alcohol and crossing the legs which have been reported as causes of neuritis.

*Prognosis*—As might be inferred from the reports in the literature and as Williamson (1924) emphatically stated, diabetic neuritis of itself does not cause death. Certainly none of my patients died of neuritis, and the duration of life after the onset of neuritis in my cases is already two and nine-tenths years even though the period of this study extended over a period of only two and one-half years. Since there are no standard criteria for the diagnosis of the neuritis and I have not specified exactly what I mean by neuritis, it is impossible to give an exact prognosis. If by neuritis one means a simple hyperglycemic pain along a nerve course, the prognosis is excellent, but if by neuritis one includes all the neurologic symptoms and signs not due to another obvious cause, the prognosis is different. Furthermore, symptoms may disappear and later reappear. Are they due to the same agent as the previous attack or to a separate process? Sometimes symptoms disappear and minor signs remain. Is the neuritis cured or not? Sometimes complete inca-

capacity lasts for a few months, and then improvement occurs fairly rapidly, so that the patient can carry out the usual activities without too much discomfort or inconvenience, yet some symptoms and signs persist practically unchanged for a period of years. Can one say that the neuritis was cured and that the changes persisting are due merely to chronic degenerative changes? The question is difficult to answer. I believe that in some cases there is only the degenerative process and in others there is a separate and distinct process resembling real neuritis but that even in the latter the degenerative changes are prone to occur and thus modify the picture produced by the neuritis itself. Since there are degrees of severity of each process and no constant picture characteristic of either, it is at times impossible to state just when each process began, when it ended and what changes it produced. This being so, the difficulty of stating the prognosis for the cases with neuritis becomes obvious. Furthermore, the prognosis depends at least partially on the etiologic factors present. If the neuritis has merely a diabetic background and a definite mechanical precipitating cause, such as pressure, recovery is apt to ensue fairly promptly (in a few weeks), although it may be delayed for some months.

**Prognosis for Symptoms** I agree with Parker (1928) that in general the prognosis is good, and recovery from the severe symptoms and disabling condition is almost certain. Seldom do severe symptoms persist for more than a few months. In those cases with sensory disturbance and marked hyperglycemia, improvement sometimes begins within a few days after the diabetes is regulated. In 1 case, however, the pain which began abruptly practically disappeared within thirty-six hours without any treatment. Certainly treatment has not brought about rapid recovery in the majority of cases, nor does improvement begin immediately after the institution of diabetic treatment, as Root and Rogers (1930) stated. It is discouraging to both the physician and the patient to note the slow response to treatment in many cases, especially in those in which the patient has a nervous temperament and shows psychic depression. In about 50 per cent of the cases improvement begins within two weeks after treatment is initiated, but in some relapse occurs shortly after the patient leaves the hospital. As Stewart (1925) and Root and Rogers (1930) remarked, the longer the duration prior to treatment, the longer delayed will be the improvement, but there are many exceptions to this. Major (1924) reported a case of diabetic tabes in which cure resulted in seven weeks by diabetic treatment, but he did not state that the ankle jerks returned and the sluggish pupils became normal. On the average, my patients did not yield to treatment in such a short period. In 47 of the cases, in which I may say that the neuritis has disappeared, the average duration of the neuritis after the initiation of treatment was eight-tenths year. Some patients

responded to treatment so well that they became symptom-free within from a week to ten days, and others still suffered to some extent more than two years after treatment was begun

**Prognosis for Signs** That the signs as well as the symptoms of diabetic neuritis disappear is recognized Pitres and Marchand (1917) said that the neuritis, even in a severe form, is cured in a few months without persistent infirmities, although Fletcher (1925) stated that improvement of motor and sensory changes is unlikely Bouchard (1884), Raven (1887), Woltman and Wilder (1929) and Schmidt (1930) reported the return of knee jerks in diabetic patients Kraus (1920) mentioned rare improvement in the reflexes Nolting and his associates (1926) reported a case with improvement in the knee jerks and return of the ankle jerks as the neuritis improved In Angle's (1928) case of diabetic tabes there was improvement and the leg reflexes returned when a diet with a moderate carbohydrate content was substituted for the previous diet low in carbohydrates, and this occurred under similar circumstances in my case 8,166 in spite of persistent hyperglycemia and hypercholesteremia Holt (1928) reported improvement in cutaneous sensitivity of the feet in a diabetic patient previously suffering from trophic changes in the feet Marinesco (1895) noted return of the left knee jerk in a diabetic patient suffering from hemiplegia Auché (1890) described signs of regeneration in diabetic nerves, as did Woltman and Wilder (1929) in 1 case, and Nicolescu and Raileanu (1926, 1927) noted signs of regeneration in the brains of diabetic patients Two of my patients (cases 6,331 and 11,106) had a normal ankle jerk on the side of hemiplegia and absence of the ankle jerk on the opposite side, but I do not know the condition of the ankle jerks prior to apoplexy In 12 other patients there was an improvement in sluggish tendon jerks or a return of reflexes, which previously were not present In 2 of these (cases 8,428 and 10,133) there was marked improvement in the position sense of the great toe as the neuritis improved, and in the former there was also partial recovery from cutaneous anesthesia of a part of the lower portion of the leg and foot One patient (case 2,843) also regained sensitivity to touch The period of improvement varied considerably In 1 case (case 8,166), seven years after the onset of the neuritis the knee jerks, previously absent, were obtained with difficulty and two years later they were easily elicited Usually recovery occurs in much less time, in the course of a year or less In 2 cases (cases 7,538 and 11,036) mere regulation of the diabetes was accompanied by return of the knee jerk and improvement in a sluggish ankle jerk, respectively In 1 case (case 4,118) in which the neuritis was characterized by absence of the left knee jerk in April, there was a sluggish response in November of the same year and an almost normal response in May of the following year

This change in reflexes was not accompanied by a corresponding change in the nutrition or health of the patient. Similarly in the other cases studied, the activity of the reflexes was not related to the nutrition except as the latter was influenced by the neuritis. It seems reasonable to assume that if lost reflexes and sensation return the nerves are not destroyed but merely damaged and complete recovery is possible.

**Prognosis of Special Features** Moore (1921) and Francis and Koenig (1926) agreed that diabetic retrobulbar neuritis responds well to treatment. My 2 patients with neuritis of the optic nerve both recovered without special treatment. Patients with paralysis of the oculomotor nerve also improve. Collier (1930) said that in most cases recovery is complete and rapid, especially in those in which insulin is administered. My patients with paralysis of the facial nerve, deafness and abdominal symptoms improved over a period of months. No improvement in pupillary reaction has been noted. In the cases of disturbance of the bladder with only slight incontinence and no retention there is a tendency to improvement as the associated neuritis improves. In the cases with marked retention the difficulty has persisted, even for some years. The psychic depression parallels the neuritis, arising usually in the course of the neuritis and disappearing with it. The condition in the cases of diabetes with an associated psychosis reported by Laudenheimer (1896), Ingegneros (1905), Pike (1921), Bostock (1926) and Reiter (1926) also improved with treatment for diabetes.

**Treatment**—Treat the diabetes first, last and all the time. Treatment must be aggressive and persistent until the disease is controlled. Not the sugar content of the blood alone, but all the chemical conditions and the physical status, must be set right. Fletcher (1925) and Nolting and his associates (1926) expressed the belief that a persistently normal value for blood sugar is essential to recovery. The diet should contain a large amount of vitamin foods, fruits, green vegetables and dairy products. Meat, eggs and cereals are included in moderate amounts. The allowance of carbohydrate is at least 120 Gm. and not more than 200 Gm., not counting the antiketogenic portion of protein and fat.

If the neuritis arises shortly after the initiation of insulin therapy and has no other obvious cause, one should substitute a brand of insulin to which the patient is not sensitive.

Barker (1930) advised diaphoresis, regulation of the bowels, control of infectious processes, hot applications, sedatives, massage and electrical treatment. I have noted that heat, usually applied by means of an electric baker or warm baths, is the best agent for the relief of pain. Since the pain is of greatest severity at night, the treatments are given in the afternoon and late evening. In severe cases warm baths can be given during the night. Sun-baths have been of help and 1 patient was much relieved by covering himself with sand and basking in the sun at

a beach Warm but light bedclothes are of help, and 1 woman (case 10,216) received relief only by wrapping the entire leg in a blanket each night Massage is at times very effective Four of my patients thought it beneficial, but another (case 9,446) said that it increased rather than decreased the symptoms Buerger's exercises should be prescribed for pain in the legs, or paresthesia, and poor circulation, as occasionally the exercises give marked relief even from the first trial Paresthesia of the feet is more likely to be relieved by such exercises than by any other measure One patient with pernicious anemia obtained relief from numbness of the hands when she soaked them daily in an astringent solution In a recent case (case 11,075) without anemia this method was of no benefit during the seventeen days during which the patient was observed I shall be interested to know what occurs in the future However, it hardly seems reasonable to use a method which may decrease the sensitivity of the skin and thereby lead to a chance injury Root and Rogers (1930) stated that absolute rest in bed is essential in the early stages of pain, a statement with which I do not entirely agree Patients who stayed in bed did not always obtain relief, and 1 woman remained in bed for several months without relief Many patients have learned that some exercise gives relief, and 1 patient refused to stay in bed because to do so caused severe pain I am inclined to give the patient something to do, to apportion the day into periods of rest and some exercise, however slight On the other hand, some patients with circulatory deficiency of the legs are considerably relieved while in bed Salicylates and hypnotics are administered when necessary, but, knowing the protracted nature of the condition in some cases, I believe that opiates should be administered sparingly if not omitted entirely

Electrical treatment for neuritis has been advised for many years<sup>25</sup> Davies (1914) obtained good results with galvanism, and Piontkowsky (1930) noted recently that galvanism stimulates recovery in the severed sciatic nerves of guinea-pigs My one experience with the use of the galvanic current was not happy, as the patient (case 5,841) stated that it increased his symptoms

In the patients with paresis the condition has improved with baking and passive and active exercise of the muscles involved For bedridden patients pillows have been used to take the pressure off the affected nerves I shortened the stay in bed as much as possible in those cases In 1 case (case 10,553), in which there was sensory neuritis of the external popliteal nerve, four days' rest in bed did not lead to paresis, however

Attention to the general condition of the patient and to all special conditions, such as anemia, foci of infection and constipation, is given

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25 Althaus (1890) Somerville (1914) Martin (1926)

I believe it important that frequent contact with the patient be maintained, both to insure the proper execution of orders given and to reassure and encourage him. Patients with depression need particular attention, and a little encouragement sometimes seems more effective than much treatment. Sioli (1932) commented on the need for proper psychic handling of diabetic patients. One patient admitted that will-power did more for him than anything else. Another patient improved in the hospital, had a relapse at home for which even morphine gave little relief and yet improved rapidly in the hospital a second time without morphine and without any change in the regimen previously followed at home.

Accessory food substances have been given to some patients. Yeast alone was given in 5 cases, in 3 of which recovery followed an average duration of the neuritis of nine-tenths year, as opposed to eight-tenths year for the series as a whole. Similarly, in the 7 cases in which liver or liver extract alone was given, recovery occurred in only 1 case, and the neuritis lasted one year. Cod liver oil alone was given in 5 cases, in 2 of which recovery took place in an average of five-tenths year. Cod liver oil and yeast together were given in 7 cases, in only 1 of which cure was accomplished and after a duration of nine-tenths year. Yeast and liver together were given in 4 cases, in 2 of which recovery occurred in an average of one and five-tenths years. All three substances were given in 4 cases, in 3 of which recovery has not yet occurred, but in the fourth the patient was relieved of the pain in six weeks by wrapping the affected leg in a blanket at night. The results of this dietary treatment are too inexact and meager to warrant drawing more than a tentative, general conclusion that it is not apparent that cod liver oil, yeast or liver is necessary for recovery or even hastens recovery. In many cases recovery occurred without any such treatment. The diabetic diets and the previous diets on which the patients had lived were apparently fully adequate for normal nutrition provided the patients could utilize them. On the other hand, the evidence is not conclusive that these substances are not helpful. One cannot judge by the symptoms how severe the changes are in the nerves (Woltman and Wilder, 1929), and it is possible that the patients given these substances would have been worse without them.

Prophylactic treatment for neuritis is hardly recognized. Aggressive treatment of the diabetes is the prime factor. So far as possible the patient should be brought back to a normal state. The bedridden patient should be protected from pressure on the nerves and from too great inactivity, and all patients with diabetes should be cautioned to refrain from crossing the legs. Patients with a fracture and others for whom inactivity and immobilization are necessary must be treated with great care and must be allowed some use of the diseased part as soon



as practicable Pressure of any sort along the course of a nerve or artery is to be avoided Patients with pernicious anemia should be carefully watched and treated to prevent involvement of the nervous system Removal of foci of infection and attention to the general condition of the patient may be of help

One prophylactic feature applies to complications rather than to the neuritis itself I have commented on the hypesthesia and the apparent ease with which the skin of many patients with hyperesthesia is damaged The use of hot water bags, especially of the chemical type is interdicted or is permitted only with careful supervision by a responsible person Heat must be applied with great care and the trimming of nails, corns and calluses must be done by a competent person who knows the susceptibility of the diabetic person to injury One cannot forget the young man who sacrificed a toe and months of activity for the sake of a short nap It would have been far better had he borne his pain a little longer and not resorted to the electric pad which wrought so much damage in such a little while

#### SUMMARY AND CONCLUSIONS

Two hundred and twenty-six persons with diabetes with neuritic manifestations were studied In this series I noted manifestations of three types (*a*) hyperglycemic, (*b*) degenerative and (*c*) neuritic

The 34 cases of the hyperglycemic type were characterized by neuritic symptoms with almost no sign The diabetes was uncontrolled at the onset of the symptoms in each case Hyperglycemia and glycosuria were the only detected diabetic factors present in every case Except in 2 cases no accessory factors were noted Regulation of the diabetes gave relief within a few days A more serious neuropathy developed subsequently in 4 cases

The frequency of this neuropathy is not indicated by its proportion of the 226 cases studied It is a common condition affecting both young and old persons with diabetes Thirty-four cases were chosen at random from many that were observed in the clinic

Forty-five cases of diabetes with relatively mild chronic neuropathy were observed To these were added 27 cases considered separately as of the circulatory type at first, because of markedly sluggish circulation in the legs There were evidences however of chronic lesions elsewhere than in the legs, and in etiology manifestations and prognosis the condition seemed to be of the same type as that in the original 45 cases Hence, the groups were combined The outstanding symptoms were pain, cramps and paresthesia of greatest intensity at night The signs included hyporeflexia and areflexia, muscular paresis, tenderness of nerves and muscles, hypesthesia, abnormal pupillary reactions and paresis of the muscles of the bladder The legs were involved more

frequently than any other part of the body. Although usually progressive over a long period of time, the neuropathy occasionally improved considerably. The process occurred in patients 40 years old or more, and arteriosclerosis was present in every case. The diabetic factor at fault was not detected. Regulation of the diabetes, use of Buerger's exercises, application of heat and prevention of lesions of the legs requiring surgical intervention constituted the chief means of treatment. As judged by sluggishness or absence of tendon reflexes of the legs, this type of neuropathy involves over 40 per cent of all diabetic patients.

One hundred and twenty cases of diabetes with relatively acute and usually severe neuropathy were studied. These represented the cases of diabetic neuritis and diabetic tabes. Among 1,000 consecutive cases of diabetes observed during a period of less than two and one-half years, there were 25 cases of neuritis. The neuropathy involved the legs in over 65 per cent of the cases. Pain, paresthesia, hyporeflexia and areflexia, muscular paresis, tenderness of the nerves and muscles, hypesthesia and hyperesthesia were the most frequent manifestations. The symptoms were much more intense at night than in the day. Fever and leukocytosis occurred not infrequently. The spinal fluid contained excess protein.

Special features included Argyll Robertson pupils, neuritis of the optic nerve, acute abdominal symptoms, paresis of the muscles of the bladder and psychic disturbances.

The neuritis affected old, rather than young patients. The diabetic factor responsible was not detected, but hyperglycemia did not appear to be essential for the production of the neuritis. Evidence of vascular disease, primarily arteriosclerosis, was present in 95.8 per cent of the 120 cases. Although presumably playing a causative rôle, the arteriosclerosis may be the result of the diabetic factor which produces the neuropathy. Pressure was apparently a precipitating cause in a number of cases. Focal infection, alcoholism and sensitivity to insulin may have led to the neuritis in a few cases. Deficient dietary intake seemed of no significance, as judged by the dietary histories and the results of feeding accessory food substances.

The prognosis is good, marked improvement occurring within a few weeks in many cases and within a few months in most cases. Improvement in the signs, as well as in the symptoms, was noted at times. However, urinary retention in cases with paralysis of the bladder persisted indefinitely. Paresis of skeletal muscle usually improved rapidly and disappeared entirely. Abnormal tendon reflexes and cutaneous sensitivity often improved.

Diligent and persistent treatment of the diabetes should be given in all cases. Correction of any suspected causative factors should be

attempted Buerger's exercises are beneficial in cases with circulatory deficiency The application of heat has been my best sedative, but burns must be avoided

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# "REST" AND "ACTIVITY" LEVELS OF LEUKOCYTES IN HEALTH AND IN DISEASE

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There are three factors of importance which have a direct bearing on the pathologic significance of any given laboratory test (1) the accuracy of the technical procedure used in the test, (2) the establishment of normal limits within which variations may occur which have no especial significance, and (3) the interpretation of the findings obtained. In establishing the normal limits attention must be given to the obtaining of a large enough aggregate of samples from a truly representative group to warrant acceptance of the limits found as a fair representation of normal variations. To be of any real importance any interpretation of an abnormal finding must be based on a sound comprehension of the pathogenesis of the disease process under consideration.

All these factors are of real importance when use is made of the leukocyte count. In a previous article<sup>1</sup> the fact was emphasized that a uniformity of technic is necessary. Even with careful dilution of the blood and thorough shaking after dilution, it was found advisable to take two samples from the diluted blood for counting if a more uniform result for the total leukocyte count is to be obtained. With carefully made cover slip smears the counting of at least 400 leukocytes was necessary to obtain a more nearly accurate differential count. Even with careful technic variations in the leukocytic picture were observed which led to a study of the limits to which these fluctuations could go before significance could be placed on them. The results obtained showed that a variation of 50 per cent in the total and up to 10 per cent in the differential count has to be allowed as a normal variation which had no especial significance. It was found that variations within these limits were present in persons on whom counts were taken at from five to ten minute intervals over a period of an hour or two. Such variation occurred at irregular and unpredictable periods. This led to the conclusion that the leukocytes were unevenly mixed in the circulating blood. In that study about 500 leukocyte counts on 25 care-

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From the Hegeman Memorial Research Laboratory of the Metropolitan Life Insurance Company Sanatorium

1 Medlar, E M. Extent of Variations in Leukocytes of Normal Individuals, *Am J M Sc* **177** 72 (Jan) 1929

fully chosen subjects were made, and I considered that the data obtained were sufficient to warrant their being accepted as a fair representation

The presence of such variations having been established in carefully selected normal persons, it became necessary to determine whether similar variations were present in persons who were ill and, if so, whether the fluctuations might invalidate the pathologic interpretation placed on the counts. An investigation along this line was carried out on patients with tuberculosis.<sup>2</sup> The results obtained showed that the fluctuations in the total leukocyte counts in the patients with tuberculosis were similar to those found in normal subjects and that the variations in the differential counts were slightly less than in normal subjects. It was also found that although variations were present it was still possible to place a pathologic interpretation on leukocyte counts in patients with tuberculosis. The fluctuations observed were not sufficient to change a favorable pathologic interpretation to an unfavorable one, and vice versa.

This brief resume of my previous publications has been made to indicate that I am fully aware of the fact that care must be used when an attempt is made to interpret the significance of such a complex phenomenon as is evidenced in the circulating leukocytic picture.

Medical literature contains an increasing number of articles which deal with investigations of the leukocytic picture found under a great variety of conditions and which give interpretations from various angles of approach. To the physiologic investigator the observations naturally revolve about the "so-called" physiologic activity of the leukocytes. To the clinician and surgeon the angle of approach is the significance of the leukocytic picture as a diagnostic aid. To the pathologist the leukocytes are of significance as a reflection of the status of the pathologic process in those conditions wherein the various types of leukocytes are known to play a prominent rôle. From whatever angle an approach to the study of leukocytic reactions is made the fundamental phenomena that must be accepted as facts are as follows: 1. There is no such thing as an absolutely constant leukocyte level, either in the total count or in the differential percentage. 2. Fluctuations in the leukocytic picture are found to be inconsistent. 3. There must occur a fluctuation of more than 50 per cent in the total count and of over 8 per cent in the differential picture before much significance can be placed on it. Furthermore, if such a change is found it must persist in subsequent observations if any real reliance is to be placed on the deviation.

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<sup>2</sup> Medlar, E. M. Evaluation of Leucocytic Reaction in Blood as Found in Cases of Tuberculosis, *Am Rev Tuberc* **20** 312 (Sept.) 1929.

There has arisen a belief that the average leukocyte count is not reliable because of the fact that variations have been observed at different times of the day, after meals and after psychologic disturbances, such as sudden fright, under conditions of "rest" and of "activity," and after successive leukocyte counts on subjects at short intervals. It is certain that if the leukocyte count is to be used as a routine test it is very necessary to determine whether such variations warrant a discontinuance of the test or whether when allowance is made for the fluctuations the test may still be relied on.

One of the major problems in research that has occupied my attention since 1927 has been the study of the leukocytic reaction in patients with tuberculosis. During this period an average of 500 leukocyte counts per month have been made. These counts have been taken on patients confined strictly to bed as well as on those who have had unlimited mild exercise. With such a volume of work it has become an established routine to take the samples of blood between 8 30 and 10 00 a m. And the variations that may occur during this interval of time have been determined by taking samples of blood from patients at ten minute intervals over this period. One factor which it did not appear to be necessary to consider has been brought up by the work of Garrey and Butler<sup>3</sup>. From their investigations they came to the conclusion that there are definite "rest" and "activity" levels of leukocytes. Since many of the patients examined in the present study were at rest and many others were active, it seemed desirable to determine whether the observations of Garrey and Butler would make it necessary to take into account the fact that a patient was in bed or engaged in exercise when an interpretation was placed on the type of leukocytic reaction found.

#### EXPERIMENTATION

In the investigations 15 members of the staff not having tuberculosis were used as controls for 37 patients with tuberculosis. During the study 854 total and 776 differential leukocyte counts were made on these subjects, or an average of about 16 per person.

The first part of the study was concerned with a comparison of the leukocytic picture after a night's rest with that when the subject had settled down to his daily routine after breakfast. Three counts at ten minute intervals were taken between 6 30 and 7 00 a m, and a similar series was obtained between 8 00 and 9 00 a m on 10 members of the staff. These observations were repeated on three consecutive days. On 25 patients with tuberculosis 2 early and 2 late counts were made on two consecutive days, and in a few instances as many counts were made as on the normal subjects. The cases of the patients with tuberculosis were divided into two groups, one, 15 cases, in which an unfavorable pathologic inter-

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3 (a) Garrey, W. E. Basal Leukocyte Count and Physiologic Leukocytosis, *Proc. Staff Meet. Mayo Clinic* **4** 157, 1929. (b) Garrey, W. E., and Butler, V. Digestive Leukocytosis Question, *Am. J. Physiol.* **100** 351, 1932.

pretation, according to the leukocytic picture, had been made, and the other, 10 cases, in which the pathologic interpretation was favorable. In the majority of instances the early samples were taken at a time when the patient had to be awakened for the tests to be made. In no instance was the subject allowed to get out of bed during this period of investigation. A total of 292 total and differential leukocyte counts were made during the study.

The results of this investigation are shown in table 1. In this table are given the distribution of the total counts, of the percentages of neutrophils, lymphocytes and monocytes and of the leukocytic indexes for the normal subjects and for the patients with tuberculosis for whom the pathologic interpretation was favorable and unfavorable, respectively, during the period of rest and of activity. At the bottom of each column is given the average total count, the average percentage and the average leukocytic index for the respective columns.

It will be noted that in each group the average total count and the percentages of lymphocytes and monocytes were higher on awakening. The average percentage of neutrophils and the leukocytic index were higher during activity. The degree of change was approximately the same in the subjects not having tuberculosis as in the patients with tuberculosis. In other words, the variations observed were independent of a pathologic process.

It will be noted that the "spread" in the leukocytic picture was greatest in the group of normal subjects. This was due in large part to the fact that 2 of the members of the group became ill during the period of investigation. One contracted severe bronchitis and the other severe diarrhea owing to indiscretion in eating. These 2 subjects account for 120 out of 192 instances in which one or another part of the leukocytic picture went beyond the normal limits of leukocyte counts.

The fact of most significance revealed by this table is that in the patients with tuberculosis in whom the disturbing factors occurring in the group of normal subjects were absent, the shift in the leukocytic index did not alter to an appreciable extent the pathologic interpretation of the leukocytic picture. The leukocytic index is a summation of the leukocytic picture as a whole. The method of obtaining and of interpreting the index has been presented in a previous communication,<sup>4</sup> to which the reader is referred.

The second part of the study was concerned with the "rest" and "activity" levels of the number of leukocytes during the time of the morning in which the routine leukocyte counts were taken. For this investigation 8 staff members, 8 ambulatory patients with tuberculosis and 4 patients who had clinically severe tuberculosis and consequently were confined to bed were selected. All patients were chosen without any reference to previous leukocyte counts. The clinical staff selected the patients with tuberculosis, and the members of the staff chosen had a good health record and no evidence of tuberculosis.

The procedure with all subjects was as follows. No change in the daily routine was made up to the day on which they were to be tested. On the morning

TABLE 1—"Rest" and "Activity" Levels of Leukocytes, Showing Distribution of Total Counts, Percentages of Neutrophils, Lymphocytes and Monocytes and Leukocytic Index

Total Cell Count, Hundreds	Normal Subjects (10 Persons)		Patients with Tuberculosis			
	At Rest	Active	Unfavorable (15 Persons)		Favorable (10 Persons)	
			At Rest	Active	At Rest	Active
Total Leukocyte Counts						
Total	90	90	62	62	44	44
41 - 50	4	3	3	3	7	12
51 - 60	7	7	7	8	12	10
61 - 70	13	25	11	16	15	12
71 - 80	22	10	9	9	5	4
81 - 90	13	16	8	7		5
91 -100	12	13	10	8	1	
101 -110	7	7	5	4	3	1
111 -120	4	6	3	5		
121 -130	6		5	2		
131 -140	1		1		1	
141 -150		1				
151 -160	1	1				
161 -170						
171 -180		1				
Average	8,377	7,377	8,338	7,887	6,522	6,136
Neutrophils, Percentage						
Neutrophils						
Total	90	90	62	62	44	44
31 - 35					6	2
36 - 40	6	2			7	2
41 - 45	9	3			5	7
46 - 50	14	8			8	7
51 - 55	24	12	5		12	11
56 - 60	18	19	11	1	6	7
61 - 65	6	12	21	11		8
66 - 70	5	15	18	21		
71 - 75	2	10	7	20		
76 - 80	4	6		8		
81 - 85	2			1		
86 - 90		3				
Average	54 94	61 83	63 88	69 45	44 02	51 63
Lymphocytes, Percentage						
Lymphocytes						
Total	90	90	62	62	44	44
6 - 10	2	2	2	6		
11 - 15	5	6	8	7		
16 - 20	2	9	16	30		
21 - 25	8	17	21	14		6
26 - 30	14	15	10	5	6	7
31 - 35	22	25	5		7	10
36 - 40	27	11			10	5
41 - 45	9	4			8	10
46 - 50					7	3
51 - 55	1				4	3
Average	32 20	27 66	21 53	18 03	49 95	35 38
Monocytes, Percentage						
Monocytes						
Total	90	90	62	62	44	44
0 - 5	2	10		9	1	7
6 - 10	71	87	42	46	30	35
11 - 15	19	3	18	7	13	2
16 - 20			2			
Average	8 66	7 68	9 77	7 60	9 35	7 35
Leukocytic Index						
Leukocytic Index						
Total	90	90	62	62	44	44
0 - 10	39	18			30	20
11 - 20	27	26	6		13	12
21 - 30	12	21	22	11	1	11
31 - 40	4	11	23	24		1
41 - 50	2	5	8	19		
51 - 60	1	3	3	5		
61 - 70	2	3		2		
71 - 80	1			1		
81 - 90						
91 -100	2	3				
Average	17 72	25 51	32 27	40 01	8 56	13 70



of the tests they were all given breakfast at 7 30 a m The members of the staff and the ambulatory patients went to the main dining room, as usual, for their breakfast and pursued the customary routine, up and about, until 8 00 a m, when three consecutive samples were taken at ten minute intervals At 8 30 all undressed and went back to bed They were instructed to relax completely and, if possible, to go to sleep During the morning 5 of the staff and 3 of the patients with tuberculosis succeeded in going into sound slumber All cooperated very well, and there was no untoward psychologic reaction to the numerous examinations Beginning at 9 a m sampling of the blood was started again and it was continued at ten minute intervals up to 11 a m The subjects then arose, dressed and went about their routine procedures until 11 20, when 3 more samples of blood were taken at ten minute intervals The patients very ill with tuberculosis had their routine changed in no way except that their breakfast was served half an hour earlier than usual

In this part of the study 380 total and differential leukocyte counts were taken The samples of blood were all taken by competent and experienced assistants The large majority of the differential counts were made by me, the rest being done by competent assistants

The findings in this study are given in table 2, which shows the distribution of the total count, of the percentages of neutrophils, lymphocytes and monocytes, and of the leukocytic index for each of the three groups At the bottom of the table is given the average for each respective column Each group is taken as a whole because it seemed reasonable that if there happened to be a significant difference between the values for the rest period and those for the activity periods the whole group would reveal it better than a single subject

A careful study of the data in this table shows that there was a slight but insignificant difference between the values for the rest period and those for the activity periods of the staff and the ambulatory patients There was also a comparable change in the group of patients with tuberculosis who were constantly at rest in bed The difference may be accounted for by the fact that 13 samples taken during the rest period were compared with 3 samples taken before and the same number taken after the rest period Had it been possible to obtain the same number of samples for each period the differences noted would in all probability have disappeared The leukocyte counts taken at 8 a m were well within normal variations of those taken at 11 20 a m The change that occurred in the leukocytic indexes during the three periods was not sufficient to alter the interpretation of the pathologic significance of the leukocytic picture in the patients with tuberculosis

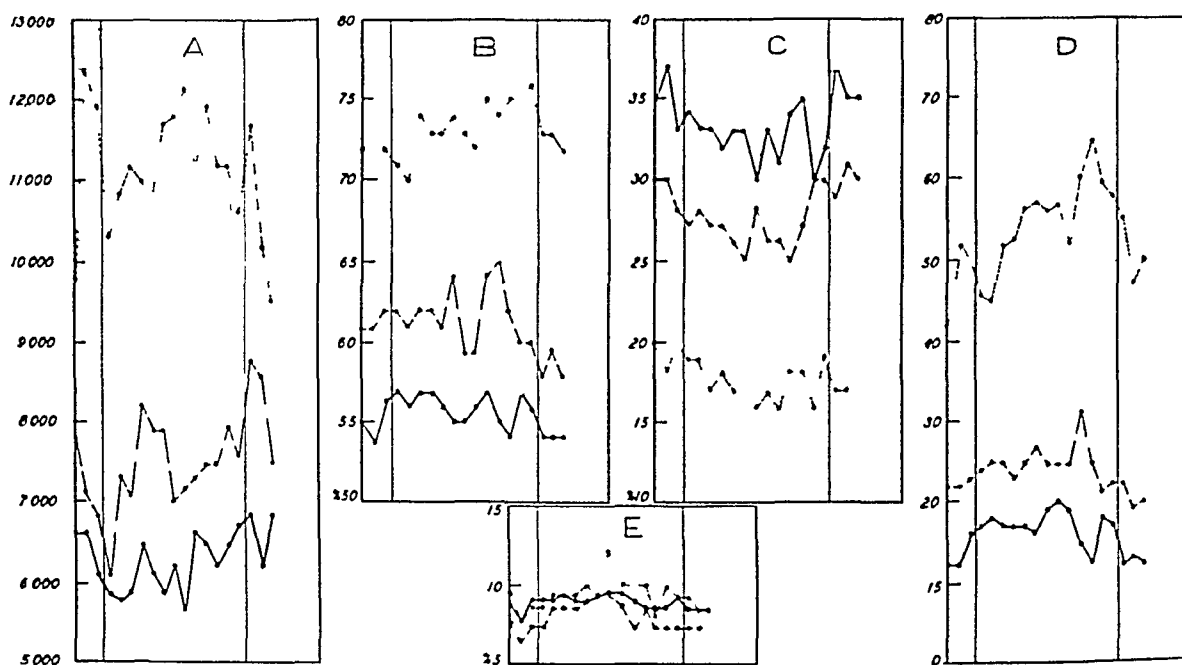
In the figure are shown the graphs for the total count, the percentages of neutrophils, lymphocytes and monocytes and the leukocytic index These graphs represent the averages obtained for each group The vertical lines indicate the time of retiring and of arising for the staff and the ambulatory patients The dots in the graphs represent the ten minute intervals at which the samples of blood were taken All of the graphs show a greater irregularity during the rest period than during

**TABLE 2—"Rest" and "Activity" Levels of Leukocytes Showing Distribution of Total Counts, Percentages of Neutrophils, Lymphocytes and Monocytes and Leukocytic Index**

Total Cell Count, Hundreds	Patients with Tuberculosis								
	Normal Subjects (8 Persons)			Ambulatory (8 Persons)			Bedfast (4 Persons)		
	8 00 to 8 20 a m	9 00 to 11 00 a m	11 20 to 11 40 a m	8 00 to 8 20 a m	9 00 to 11 00 a m	11 20 to 11 40 a m	8 00 to 8 20 a m	9 00 to 11 00 a m	11 20 to 11 40 a m
	Total Leukocyte Counts								
Total	24	104	24	24	104	24	12	52	12
31 - 40		4			2				
41 - 50	3	26	3	3	7				
51 - 60	8	17	3	3	17	4			
61 - 70	7	32	11	5	16	3		4	1
71 - 80	5	20	2	5	26	3	1	9	
81 - 90	1	3	4	5	17	5	2	4	3
91 -100		2	1	3	15	5	1	8	4
101 -110						2	2	7	
111 -120					3	2	3	2	1
121 -130							1	4	1
131 -140								2	1
141 -150								3	
151 -160							1	2	1
161 -170								2	
171 -180							1	3	
181 -190								1	
191 -200									
201 -210								1	
Average	6,238	5,886	6,715	7,113	7,309	8,300	10,400	11,126	10,383
Neutrophils, Percentage	Neutrophils								
Total	24	104	24	24	104	24	12	52	12
41 - 45		6	3			2			
46 - 50	8	15	3	3	20	6			
51 - 55	4	26	9	9	23	7			
56 - 60	6	32	8	6	25	3			
61 - 65	6	20	1	4	17	3	2	3	2
66 - 70		5		2	5	2	3	13	2
71 - 75					7	1	2	16	3
76 - 80					2		4	18	5
81 - 85							1	2	
86 - 90									
Average	55 08	55 69	53 21	61 54	62 42	59 87	72 58	73 23	72 91
Lymphocytes, Percentage	Lymphocytes								
Total	24	104	24	24	104	24	12	52	12
6 - 10							2	7	
11 - 15					6		2	16	6
16 - 20				1	16	2	3	16	3
21 - 25		6		7	20	6	2	3	1
26 - 30	7	33	3	6	25	1	3	10	2
31 - 35	8	46	11	5	28	9			
36 - 40	8	15	7	5	9	6			
41 - 45	1	4	3						
Average	33 62	30 94	32 75	29 25	26 84	30 29	18 83	17 32	17 67
Monocytes, Percentage	Monocytes								
Total	24	104	24	24	104	24	12	52	12
0 - 5	3	11		7	6	6	2	4	1
6 - 10	21	79	24	17	89	18	10	33	10
11 - 15		14			9			10	1
Average	7 31	8 09	8 00	6 4	8 09	6 62	7 05	8 24	7 95
Leukocytic Index	Leukocytic Index								
Total	24	104	24	24	104	24	12	52	12
0 - 10	10	19	11	3	9	5			
11 - 20	8	49	11	8	34	10			
21 - 30	6	36	2	10	36	6	3	13	3
31 - 40				3	12	1	2		1
41 - 50					7	2	2	7	1
51 - 60					2		2	14	1
61 - 70					3		1	7	5
71 - 80					1			4	1
81 - 90							2	2	
91 -100								5	
Average	13 62	17 03	11 52	20 85	25 17	19 44	48 83	54 54	51 33

the period of activity This comparison, however, can hardly be considered valid because of the difference in the number of the samples compared Whatever variations are present come well within a 50 per cent fluctuation in the total and a 10 per cent change in the differential count, which I observed in healthy normal persons when samples of blood are taken at from five to ten minute intervals over a period of one to two hours The fluctuations that occurred in the leukocytic index as shown in the graphs do not essentially alter the pathologic interpretation of the leukocytic picture for each group as a whole

From a careful study of the records of individual subjects I gained the impression that the abnormal procedure of returning to bed after



Graphs showing the averages for *A*, the total counts, *B*, the percentage of neutrophils, *C*, the percentage of lymphocytes, *D*, the leukocytic index, and *E*, the percentage of monocytes The space between the vertical lines represents the time normal subjects and ambulatory patients with tuberculosis spent in bed, and the dots, the ten minute intervals at which samples of blood were taken The solid line indicates the normal subjects, the dash line the ambulatory patients with tuberculosis and the dotted line the bedfast patients with tuberculosis

breakfast instead of pursuing the ordinary routine brought about a greater instability of the leukocytic picture as a whole than I have observed in persons up and about at the same period of the day In 3 instances the neutrophil count varied to as high as 15 per cent in different persons From this it would appear to be unwise to alter radically the usual routine procedures of daily life if comparable leukocyte counts are to be obtained

Since the data presented so far do not agree with the observations of Garrey and Butler<sup>3b</sup> relative to the existence of a "rest" and an "activity" level of leukocytes, total leukocyte counts were taken on the group of normal subjects at ten minute intervals between 9 and 11 a m on two different days while they were about their usual routine duties. The purpose of this study was to compare the leukocyte count on a day at rest with that on a day at work and also those on two different days at work. All the members of the group were available for the first day, and 6 of 8 were available for the second day at work. No attempt was made to control the activities of the persons involved, and no one knew the day on which the tests were to be made. One hundred and eighty-two total counts were taken with the subjects at their routine tasks. One assistant obtained all the samples of blood, and I made all the total counts. The results are given in table 3.

TABLE 3—*Rest and Activity Level of Leukocytes*

Total Cell Count, Hundreds	Total Leukocyte Counts (10 Minute Intervals from 9 to 11 a m)			
	Eight Normal Subjects		Six Normal Subjects	
	At Work from 9 to 11 a m	In Bed from 8 30 to 11 a m	At Work from 9 to 11 a m	At Work from 9 to 11 a m
	104	104	78	76
Total				
31 40	1	4	1	
41 50	18	26	14	4
51 - 60	25	17	18	9
61 70	21	32	17	26
71 80	16	20	11	12
81 90	16	3	11	17
91 100	6	2	5	6
101 110	1		1	4
111 120				
Average	6,236	5,886	6,204	7,242

It will be noted that there is a greater difference between the leukocyte counts on the two days at work than there is between those taken on the first day at work and those on the day in bed. None of these subjects, whether in bed or at work, showed a variation of less than 1,500 cells, and most of them showed a variation of between 2,000 and 4,000 cells. From this study it would appear illogical to attempt to compare too closely leukocyte counts of a subject from day to day. Rather it would seem that any variation of the total count within 50 per cent must be accepted as a normal variation under all conditions, whether the subject is at rest, at work or ill in bed.

#### COMMENT

Nature is always in a state of flux. All physiologic and pathologic processes are constantly in a state of ebb and flow. To determine with mathematical precision the point at which normal physiologic processes, that is health, cease and pathologic processes, that is disease, begin is hardly possible. Before any attempt is made to place an interpretation of abnormality on any phenomenon in life it is requisite that reason-

able limits within which a phenomenon may fluctuate be established as a normal variation. Within this range of fluctuation no definite conclusion relative to abnormality can be made. If a sample of sufficient size has been used to determine the limits of normality it will be found that the major portion of the samples obtained will lie within the central portion of the range with a decrease of the number of samples as the extreme limits are approached. Thus it will be possible to surmise that abnormality is being approached if on repeated examinations the samples remain at the extreme limits of this normal range. When on repeated examination the samples show that a phenomenon has passed definitely beyond the normal range abnormality may be said definitely to exist.

In studies of the leukocyte count I believe that insufficient attention has been paid to the normal range of variation. There have occurred too often in the literature communications in which definite conclusions have been drawn from changes in the leukocytic picture that are well within the normal variations. Interpreting a rise of 2 000 or 3 000 cells within a few minutes following a change in posture, a sudden mild psychologic upset or some other mild and harmless incident as due to this happening is open to serious question. I do not believe that conclusions from such data are valid. At most they can be no better than surmises, because the fluctuations noted are not beyond the normal range of variation. Such interpretations have unnecessarily thrown doubt on the significance of leukocyte counts.

Variations in the total leukocyte count undoubtedly often have been misinterpreted. My observations are in agreement with those of Garrey and Butler and others, namely, that there is often a difference in the total leukocyte count in different subjects. One person may reveal total leukocyte counts ranging from 5,000 to 7,000, whereas in another the normal range may be from 7,000 to 10,000. If single total counts are taken from day to day it may happen that the number of leukocytes per cubic millimeter on one day appears to be about 3,000 cells higher than on another day. Such reasoning would undoubtedly prove erroneous if counts were made on such persons at short intervals over an hour or so each day. This is well shown in the data in table 3. Here the difference between the averages of the 6 persons on the two days at work was only 1,000 cells per cubic millimeter. And during the period of observation on each day these subjects showed a variation of from 1,500 to 3,800 cells. It was observed that there was usually a greater variation in the total cell counts in those subjects in whom the leukocyte count was the higher. I found that the higher the total counts the greater the apparent (although the same relative) variation that occurs. Thus a shift from 15,000 to 20 000 has no greater significance than a shift from

5,000 to 7,000, if the counts are taken within a few hours. Shifts of this sort, up and down, have been observed in a subject within a period of half an hour. In one subject it was the normal variation within a normal range, whereas in the other it was a normal variation within a definitely pathologic range. In either instance no importance can be placed on the change observed.

Too much attention has been centered on the total leukocyte count. It is useful to know whether there is hyperleukocytosis, ortholeukocytosis or hypoleukocytosis of the blood. This, however, is but one part of the leukocytic picture, and it often is the most insignificant. I have at my disposal over 40,000 leukocyte counts on about 600 patients with tuberculosis. The total leukocyte counts in at least two thirds of the 40,000 counts are well within a normal range of from 5,000 to 10,000. Were much reliance placed on the total leukocyte counts, one would conclude that the leukocytic picture in tuberculosis is not significant. This would be a very erroneous conclusion. In patients with tuberculosis it is of real importance to know whether definite leukocytosis or leukopenia exists. The presence of a normal total leukocyte count is not of great significance.

The differential leukocytic picture should always be considered in conjunction with the total leukocyte count. And if it is impossible to have both, which it seldom is, the differential leukocyte count should be greatly preferred to the total count. A very common experience of mine has been to find that normal total counts in different subjects have very different differential leukocytic pictures. Thus in one person a total leukocyte count of 8,000 can show 80 per cent neutrophils and 10 per cent lymphocytes, whereas in another the same total count can have a differential picture of 50 per cent neutrophils and 40 per cent lymphocytes. The difference between these two counts is significant when a pathologic interpretation is placed on them.

A considerable number of articles have appeared in journals on physiology relative to the physiologic rôle of the leukocytes. I should like to raise the query as to whether the function of the leukocytes is physiologic. If theirs is a physiologic function, do they not deal with pathologic physiology? These cells are very common participants in pathologic processes. It seems plausible that their real function, even in a normal physiologic state, is to take care of abnormal or pathologic products formed during normal physiologic processes.

To attempt to interpret the changes found between the leukocyte counts taken after a night's rest or during complete relaxation and those taken during mild and normal activity would lead at best to nothing better than conjectures. It has occurred to me that since the blood is within a closed system of vessels might not the slowing of the rate

of blood flow and a lowering of the vascular tone lead to a more sluggish circulation? Might not this allow a more irregular distribution of the leukocytic cell types? This suggestion has also been made by Garrey<sup>3a</sup> If this is true, care should be exercised to procure samples of blood at a time when a normal vascular tone and blood flow are well established

When one considers the numerous portals of entry of the leukocytes into the circulating blood, it is not surprising that fluctuations are present in the normal leukocytic picture Nature has not provided a common collecting depot in which the leukocytes can be thoroughly mixed before they enter the main blood stream The wonder is that the variations are not greater than they are Even with the fluctuations as they exist, it is still possible to place valid interpretations on leukocytic reactions when allowance is made for the normal irregularity of distribution of the leukocytes in the circulating blood

The normal variations which I have found in the leukocytic picture do not invalidate the use of the leukocyte count in interpreting pathologic processes in which leukocytes participate I agree with the conclusion of Harvey and Hamilton,<sup>5</sup> who stated "The daily variation of cell counts is not a greatly disturbing factor to their utility"

#### CONCLUSION

1 Definite "rest" and "activity" levels of the leukocyte count do not exist if the activity is limited to mild exercise

2 Complete relaxation, such as a night's sleep or two hours in bed, appears to bring about a more irregular distribution of the leukocytes, both in the total and in the differential count, than is present during a state of normal activity

3 Great care should be exercised whenever an attempt is made to interpret the significance of the leukocytic picture when the fluctuations noted are within a normal range

4 Fluctuations occur in abnormal as well as in normal leukocytic pictures

5 These variations, when allowed for, do not seriously interfere with the pathologic interpretation of the significance of leukocyte counts

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<sup>5</sup> Harvey, W F, and Hamilton, T D Constancy of Day-to-Day Leukocyte Blood Count Medico-Statistical Study, Edinburgh M J 41 465, 1934

# SERUM CALCIUM, INORGANIC PHOSPHORUS AND PHOSPHATASE ACTIVITY

IN HYPERPARATHYROIDISM, PAGET'S DISEASE, MULTIPLE MYELOMA  
AND NEOPLASTIC DISEASE OF THE BONES

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It is now generally recognized that the determination of serum calcium, inorganic phosphorus and phosphatase activity, in conjunction with clinical and roentgenologic study, may provide evidence of value in the differential diagnosis of certain diseases of bone. It is becoming increasingly evident, however, that for adequate interpretation of the variations in these constituents of the blood, particularly as regards their significance with respect to the underlying physiologic mechanisms involved, more data are desirable. This study is concerned with a review and appraisal of the available relevant but scattered data relating to hyperparathyroidism, Paget's disease, multiple myeloma and neoplastic disease of the bones. Additional observations on personally studied cases are presented.

## METHODS

Twenty cubic centimeters of venous blood obtained from patients while fasting was transferred to a 25 cc pyrex centrifuge tube, allowed to clot for one-half hour and then centrifugated for from five to ten minutes at 1,000 revolutions per minute. The calcium content of the serum was determined in duplicate on 2 cc samples of the supernatant serum by the Clark and Collip modification<sup>1</sup> of the Kramer and Tisdall method, at least one hour being allowed for the precipitation of calcium oxalate. The inorganic phosphorus content of the serum was determined in duplicate on 1 cc samples by the method of Kuttner and Lichtenstein,<sup>2</sup> with

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1 Clark, E P, and Collip, J B. A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, *J Biol Chem* **63** 461, 1925

2 Kuttner, T, and Lichtenstein, L. Estimation of Phosphorus Molybdic Acid-Stannous Chloride Reagent, *J Biol Chem* **86** 671, 1930



correction for deviation from Beer's law<sup>3</sup> With scrums from patients with metastatic carcinoma the filtrate obtained after precipitation of protein with 5 per cent tri-chloroacetic acid was almost invariably turbid, and filtration was repeated three or four times Even then, although hardened filter-paper and a 10 per cent solution of tri-chloroacetic acid were used, it was not always possible to obtain a clear filtrate The nature of the substance causing this cloudiness, rarely encountered in other than neoplastic conditions, was not investigated further Serum phosphatase activity was determined in duplicate on the protein-free filtrate of a 1 cc sample by the Bodansky method<sup>4</sup> The determinations were made on serum, since oxalate diminishes phosphatase activity from 10 to 20 per cent<sup>5</sup> The results were expressed in Bodansky units, a unit being defined as equivalent to 1 mg of phosphorus in the form of phosphate ion liberated from a substrate of sodium beta-glycerophosphate during incubation for one hour at 37 C, at a *p*<sub>H</sub> of 8.6<sup>4</sup> When the phosphatase activity exceeded 40 Bodansky units per hundred cubic centimeters, the following positive correction was applied to the result in order to compensate for the inhibiting effect of hydrolytic products when 10 per cent or more of the substrate had been hydrolyzed<sup>6</sup>

$$E_1 = E + \frac{E^2}{1,000}$$

E represents the original value expressed in Bodansky units and *E*<sub>1</sub>, the corrected value in Bodansky units

The values obtained for the serum of normal adults by these methods have the following ranges calcium content, from 9 to 11 mg per hundred cubic centimeters, inorganic phosphorus content, from 2.7 to 4 mg, phosphatase activity, from 1.5 to 4 Bodansky units per hundred cubic centimeters<sup>4</sup> For normal children the serum phosphatase activity may be as high as 12 Bodansky units<sup>4</sup>

To obviate individual variations in technic, all the determinations of calcium, inorganic phosphate and phosphatase were made by one of us (E. B. G.) In order to avoid contamination and hemolysis, we took the samples of blood in most instances with our own equipment

The amounts of nonprotein nitrogen and, when indicated, of serum protein and bilirubin were determined by the micromethod of Folin and Wu, the macromethod of Kjeldahl and the method of Thannhauser and Andersen, respectively These analyses were made by Miss R. Jillson

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3 Bodansky, A. Phosphatase Studies. I. Determination of Inorganic Phosphate, Beer's Law and Interfering Substances in the Kuttner-Lichtenstein Method, *J. Biol. Chem.* **99** 197, 1932

4 Bodansky, A. Phosphatase Studies. II. Determination of Serum Phosphatase. Factors Influencing the Accuracy of the Determination, *J. Biol. Chem.* **101** 93, 1933

5 (a) Bodansky, A., and Jaffe, H. L. Effects of Diet and Fasting on Plasma Phosphatase, *Proc. Soc. Exper. Biol. & Med.* **29** 199, 1931. (b) O'Reilly, T. J., and Race, J. Osteitis Deformans, *Quart. J. Med.* **1** 471, 1932. (c) Gutman, A. B., and Gutman, E. B. Unpublished data. (d) Bodansky<sup>4</sup>

6 Bodansky, A., and Jaffe, H. L. Phosphatase Studies. V. Serum Phosphatase as a Criterion of the Severity and Rate of Healing of Rickets, *Am. J. Dis. Child.* **48** 1268 (Dec.) 1934

TABLE 1—*Summary of Studies of the Blood in 4 Cases of Hyperparathyroidism*

Date	Calcium, Mg per 100 Cc	Inorganic Phosphorus, Mg per 100 Cc	Phosphatase, Bodansky Units per 100 Cc	Non protein Nitrogen, Mg per 100 Cc	Protein, per Cent	Additional Data†
Case 1 (C G, Male, 34 Years)						
7/14/33	15.7	2.7	34.9			
8/1/33	15.4	2.6	34.8	39	5.7	
8/15/33	15.8	3.1	28.3	40	6.8	Magnesium, 2.1 mg, carbon dioxide, 47.3 volumes %, chloride, 111.1 milliequivalents, sodium, 139.5 milliequivalents, potassium, 5.1 milliequivalents
8/17/33	Operation					
8/18/33	9.7	2.4	32.1	47		Magnesium, 1.9 mg
8/20/33	9.2		27.9	39		Magnesium, 2.8 mg
8/21/33	8.8	1.9	29.9			
8/23/33	8.7	2.1	36.2	25		Magnesium, 3.5 mg
8/28/33	8.1	2.7	45.6			
10/6/33	9.4	4.2	16.6	51	7.2	Serum cholesterol, 336 mg
12/29/33	10.5	4.0	7.9	60	7.2	
3/16/34	10.4	4.0	6.1	60	7.0	
8/7/34	10.2	3.0	4.2	44	7.1	Serum cholesterol, 248 mg
7/23/35	10.3	2.9	4.5	50		Serum cholesterol, 268 mg
Case 2 (M W, Female, 53 Years)						
			Urea Nitrogen, Mg per 100 Cc			
6/16/32	12.4	3.9				
6/30/32	13.9	5.3			7.6	
7/8/32*	13.1	7.1	20.2	48		Uric acid, 10.1 mg, creatinine, 5 mg
7/12/32	10.5	6.1		136	7.5	Creatinine, 4.6 mg
7/20/32	8.0	5.8		132		
7/25/32	9.9	3.9		100		
7/28/32	Operation					
7/31/32	7.4	4.8		82		
8/1/32	6.4	4.1		76		
8/3/32	5.0	3.7		71		
8/8/32	6.1	1.7		65		
8/12/32*	8.2	2.6	11.5	64	5.9	
8/16/32	9.0	3.0		63		
8/19/32	9.6	2.9		64		
8/25/32	9.0	3.1		71		
9/1/32	9.6	3.4		73		
9/7/32	9.8	3.6		76		
9/12/32	9.5	3.4		75		
12/7/32*	9.2	3.1	13.8			
4/5/33*	8.9	3.9	12.1	28	6.4	Uric acid, 6.4 mg, creatinine, 2.4 mg
12/9/34	9.5	3.9	6.2			Nonprotein nitrogen, 75 mg
12/20/35	9.0	4.1	4.7			Nonprotein nitrogen, 125 mg
Case 3 (E M, Female, 46 Years)						
6/19/26	11.5	2.5				
7/1/26	12.0			17		
Case 4 (N P, Female, 60 Years)						
5/31/33				100		Creatinine, 3.3 mg
6/5/33	9.7					
6/8/33*	10.2	8.4	27.3			

\* Dr. A. Bodansky made the determinations indicated by the asterisk.

† Values are expressed in terms of milligrams per hundred cubic centimeters or milliequivalents per liter.

## HYPERPARATHYROIDISM

The results of analyses of the blood in 4 proved cases of hyperparathyroidism are summarized in table 1<sup>7</sup>. In cases 1 and 3 the characteristic findings of hypercalcemia, hypophosphatemia and increased blood phosphatase activity are presented. Cases 2 and 4, in which the amount of inorganic phosphate in the serum was increased and the calcium content was apparently normal, illustrate the effects of complicating renal insufficiency. Case 2 is of particular interest in this respect, since acute retention of nitrogen took place while the patient was under observation and the calcium level of the serum fell although no further increase in retention of phosphate was demonstrable. Case 1 illustrates also the characteristic postoperative decrease in the calcium content of the serum within twenty-four hours and the tendency of the inorganic phosphate content to remain low (or even to show a transient further decrease) for several days after operation. The blood phosphatase activity, as noted by many observers, is not immediately affected by surgical intervention but remains elevated for months or years. In case 1 a temporary increase in phosphatase activity was noted. Essentially normal values were found one year after operation. In case 2 the level of blood phosphatase was still somewhat higher than normal two and one-half years after operation. During this postoperative period the persisting elevation of blood phosphatase activity provides the only indication obtainable by studies of the blood of skeletal changes still readily apparent in roentgenograms.

A review of the literature reveals that of 156 cases of hyperparathyroidism<sup>8</sup> the results of determination of the serum calcium are recorded in 114. In 109 instances at least one value of 11 mg or more per hundred cubic centimeters was obtained. In 91 cases the calcium content of the serum consistently exceeded 12 mg. Values for the amount of inorganic phosphorus in the blood are recorded in 79 cases, in 35 of which they were consistently less than 2.5 mg per hundred cubic centimeters.

While consistent hypercalcemia with a calcium content of 12 mg or more per hundred cubic centimeters has been found in 80 per cent of the cases of hyperparathyroidism, normal values for the calcium content may be encountered even in advanced stages of the disease. In some instances impaired renal function, as evidenced by retention of nitrogen and phosphates or by postmortem study of the kidneys, probably accounts for the apparent absence of hypercal-

<sup>7</sup> Histories of the cases are reported elsewhere.<sup>9</sup>

<sup>8</sup> This series of 156 cases of hyperparathyroidism collected from the literature includes only those in which there were definite indications of parathyroid overactivity and in which one or more parathyroid adenomas were observed at operation or autopsy.

cemia<sup>9, 10</sup> (cases 2 and 4) A marked decrease in the amount of calcium in the serum, associated with retention of phosphates, is a not uncommon finding in cases of terminal uremia<sup>11</sup>

In other instances, however, nitrogen retention was not present, and the cause of the absence of hypercalcemia must be sought elsewhere Bodansky and Jaffe have shown that variations in calcium intake as well as in the dosage of parathyroid extract affect the level of the calcium content of the serum in experimental hyperparathyroidism<sup>12</sup> By the use of appropriate doses of parathyroid extract, they were able to produce typical lesions of osteitis fibrosa in the bones of young dogs on a low calcium intake without inducing hypercalcemia<sup>12</sup> There may be analogous clinical cases of slowly progressive disease in which changes in the bone characteristic of hyperparathyroidism develop without hypercalcemia The cases in which the values for serum calcium were normal in the earlier stages of the disease and in which hypercalcemia subsequently developed are of particular interest in this connection The possibility that in some cases of hyperparathyroidism in which there were normal amounts of serum calcium the disease was in remission must also be considered That depletion of available calcium reserves was not the cause of the normal values for serum calcium is suggested by the marked hypercalcemia consistently found in those cases in which extreme decalcification of the skeleton was present

It has already been pointed out that the absence of hypophosphatemia in some cases of hyperparathyroidism may be explained by the presence of renal impairment<sup>10</sup> It is uncertain whether occasional improvement in renal function after removal of a parathyroid adenoma is to be interpreted as a direct effect of the parathyroid hormone on the kidney Hyperphosphatemia is characteristic of overdosage of parathyroid extract in some animals<sup>13</sup> and in man<sup>14</sup>

The blood phosphatase activity in 28 cases of hyperparathyroidism with definite skeletal changes has been reported in the literature and

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9 Gutman, A B , Swenson, P C , and Parsons, W B The Differential Diagnosis of Hyperparathyroidism, *J A M A* **103**:87 (July 14) 1934

10 Albright, F , Aub, J C , and Bauer, W Hyperparathyroidism, *J A M A* **102** 1276 (April 21) 1934

11 Peters, J P , and Van Slyke, D D Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol 1, p 840 Gutman and Gutman<sup>5c</sup>

12 Bodansky, A , and Jaffe, H L Parathormone Dosage and Serum Calcium and Phosphorus in Experimental Chronic Hyperparathyroidism Leading to Osteitis Fibrosa, *J Exper Med* **53** 591, 1931

13 Thomson, D L , and Collip, J B The Parathyroid Glands, *Physiol Rev* **12** 309, 1932

14 Albright, F , Bauer, W , Ropes, M , and Aub, J C Studies of Calcium and Phosphorus Metabolism IV The Effect of the Parathyroid Hormone, *J Clin Investigation* **7** 139, 1929

was found to be increased in every instance The reports are summarized as follows

Year	Author	Age, Years	Sex	Blood			Increase in Phos phatase Activity
				Calcium, Mg per 100 Cc	Inorganic Phos phorus, Mg per 100 Cc	Phosphatase, Units per 100 Cc	
1929	Hunter <sup>15</sup>	41	F	12 0 16 7	1 0 2 5	1 9 Kay <sup>26</sup>	Approximately 10 times normal maximum
1931	Allan <sup>16</sup>	34	M	15 0 16 7	2 6 3 0	37 5 56 9 Allan (serum) <sup>16</sup>	4 6 times normal max imum (?)
1931	Cooley <sup>17</sup>	14	F	13 6 15 2	2 6 3 0	0 25 Kay <sup>26?</sup>	Approximately 1¼ times normal maximum
1931	Cosin <sup>18</sup>	17	M	15 3 16 5	2 2	3 1 Kay (plasma) <sup>26?</sup>	Approximately 15 times normal maximum (?)
1931	Hunter and Turnbull <sup>19</sup>	37	F	11 2 13 6	1 3	1 13 Kay (plasma) <sup>26</sup>	Approximately 6 times normal maximum
		49	F	14 4 15 0	1 8	1 16 Kay (plasma) <sup>26</sup>	Approximately 6 times normal maximum
		51	F	12 0 15 0	<2 0	1 06 Kay (plasma) <sup>26</sup>	Approximately 5 times normal maximum
1931	Quick and Hunsberger <sup>20</sup>	25	M	14 7 15 8	2 1 3 6	"Increased 4 5 fold," Kay (plasma) <sup>26</sup>	
1933	Dyke, Walker and Freeman <sup>21</sup>	14	F	17 7	2 8	42 Jenner and Kay (plasma) <sup>27</sup>	7 times normal maxi mum
1933	Keynes and Taylor <sup>22</sup>	18	M	14 7	1 5	0 31 Kay (plasma) <sup>26?</sup>	1 5 times normal maxi mum
1933	Rankin and Priestley <sup>23</sup>	47	F	10 6 11 8	2 3 3 0	61 7 Allan <sup>16?</sup>	Approximately 6 times normal maximum
1934	Albright, Aub Bauer <sup>10</sup>	13	F	12 1	4 7	36 Bodansky (plasma) <sup>28</sup>	9 times normal maxi mum
		41	F	14 2	2 3	7 5 Bodansky (plasma) <sup>28</sup>	Approximately 2 times normal maximum
		35	M	13 1 16 5	1 4 3 2	14 2 Bodansky (plasma) <sup>28</sup>	3 5 times normal maxi mum
		36	F	13 7	2 4	18 Bodansky (plasma) <sup>28</sup>	4 5 times normal maxi mum
		33	M	16 8	2 9	26 Bodansky (plasma) <sup>28</sup>	6 5 times normal maxi mum
		38	F	13 9	1 6	16 Bodansky (plasma) <sup>28</sup>	4 times normal maxi mum
		52	M	14 5	1 9	6 5 Bodansky (plasma) <sup>28</sup>	1 5 times normal maxi mum

15 Hunter, D Hyperparathyroidism (Hyperfunction of a Parathyroid Tumour in a Case of Generalized Osteitis Fibrosa), Proc Roy Soc Med (Sect Med) **23** 227, 1929

16 Allan, F N Hyperparathyroidism Report of a Case, Proc Staff Meet, Mayo Clin **6** 684, 1931

17 Cooley, T B Hyperparathyroidism and Similar Diseases of Bone, Am J Dis Child **42** 691 (Sept) 1931

18 Cosin, C F A Case of Osteitis Fibrosa Cystica with Cystic Adenoma of the Parathyroid, Guy's Hosp Rep **81** 297, 1931

19 Hunter, D, and Turnbull, H M Hyperparathyroidism Generalized Osteitis Fibrosa, Brit J Surg **19** 203, 1931

20 Quick, A J, and Hunsberger, A Hyperparathyroidism Clinical Picture in Far Advanced Stage, J A M A **96** 745 (March 7) 1931

21 Dyke, S C, Walker, R M, and Freeman, E Adenoma of the Parathyroid Associated with Generalized Osteitis Fibrosa, Lancet **2** 530, 1933

22 Keynes, G, and Taylor, H A Case of Parathyroid Tumour, Brit J Surg **21** 20, 1933

23 Rankin, F W, and Priestley, J T Tumors of the Parathyroid Gland, Am J Surg **20** 298, 1933

Year	Author	Age, Years	Sex	Blood			Increase in Phos phatase Activity
				Calcium, Mg per 100 Cc	Inorganic Phos phorus, Mg per 100 Cc	Phosphatase, Units per 100 Cc	
1934	Gutman, Swen son and Parsons <sup>8</sup>	34	M	15 4 15 8	2 6 3 1	28 3 34 9 Bodansky (serum) <sup>4</sup>	7 8 5 times normal maxi mum
		53	F	8 0 13 9	3 9 7 1	20 2 Bodansky (serum) <sup>4</sup>	5 times normal maxi mum
		60	F	9 7 10 2	8 4	27 3 Bodansky (serum) <sup>4</sup>	7 times normal maxi mum
1935	Lahey and Haggart <sup>24</sup>	62	F	"Mean 13 3"	1 7 2 3	64 4 Bodansky <sup>28?</sup>	Approximately 16 times normal maximum
		53	F	12 5 14 9	2 2 3 0	10 2 Bodansky <sup>28?</sup>	"Approximately nor mal" (?)
		74	F	Maximum 11 3, "mean 10 0"	1 9 3 0	7 2 Bodansky <sup>28?</sup>	Approximately 2 times normal maximum
		44	F	14 4 15 1	2 4 3 5	35 Bodansky <sup>28?</sup>	Approximately 9 times normal maximum
		52	F	13 8 14 1	2 0 2 1	44 8 Bodansky <sup>28?</sup>	Approximately 11 times normal maximum
1935	Castleman and Mallory <sup>25</sup>	55	F	11 36	2 53	5 75 Bodansky <sup>28?</sup>	Approximately 1½ times normal maximum
		49	M	15 01	2 61	14 1 Bodansky <sup>28?</sup>	Approximately 3½ times normal maximum

Albright, Aub and Bauer<sup>10</sup> observed essentially normal levels for blood phosphatase in a group of patients presenting renal stones, hypercalcemia and diffuse hyperplasia of the parathyroids but no demonstrable changes in the bones

In addition to the group of 156 cases of "primary" hyperparathyroidism, a state of "secondary" hyperparathyroidism has been postulated in a variety of conditions, chiefly on the basis of associated morphologic changes in the parathyroid glands or hypercalcemia. The following diseases in which complicating "secondary" hyperparathyroidism has been postulated and the evidence for the assumption are enumerated

1 Rickets. Compensatory hypertrophy of the parathyroids,<sup>29</sup> compensatory hyperplasia of the parathyroids<sup>30</sup> and evidences of an excess

24 Lahey, F. H., and Haggart, G. E. Clinical Diagnosis and the Operative Technique of Parathyroidectomy, Surg., Gynec. & Obst. **60** 1033, 1935

25 Castleman, B., and Mallory, T. B. The Pathology of the Parathyroid Gland in Hyperparathyroidism, Am. J. Path. **11** 1, 1935

26 Kay, H. D. Plasma Phosphatase in Osteitis Deformans and in Other Diseases of Bone, Brit. J. Exper. Path. **10** 253, 1929

27 Jenner, H. D., and Kay, H. D. Plasma Phosphatase. III. A Clinical Method for the Determination of Plasma Phosphatase, Brit. J. Exper. Path. **13** 22, 1932

28 Bodansky, A. Determination of Plasma Phosphatase, Proc. Soc. Exper. Biol. & Med. **28** 760, 1931

29 Erdheim, J. Rachitis und Epithelkörperchen, Vienna, Alfred Holder, 1914

30 Pappenheimer, A. M., and Minor, J. Hyperplasia of the Parathyroids in Human Rickets, J. M. Research **42** 391, 1921

of parathyroid hormone in the blood of children with rickets<sup>31</sup> have been described. The blood phosphatase activity is markedly increased<sup>32</sup>

2 Osteomalacia. There may be compensatory hypertrophy of the parathyroids<sup>29</sup>. The blood phosphatase activity is moderately increased<sup>33</sup>

3 Osteogenesis imperfecta. Occasional enlargement of the parathyroid glands has been described<sup>31</sup>. The blood phosphatase activity is normal or somewhat increased<sup>35</sup>

4 Paget's disease. The evidence was summarized by Ballin<sup>36</sup>. The blood phosphatase activity, as is shown later, is markedly increased

5 Multiple myeloma. Hypercalcemia and hypercalcaemia with questionable hyperplasia of the parathyroid have been interpreted as indicating complicating hyperparathyroidism<sup>37</sup>. The blood phosphatase activity, as is shown later, is normal or slightly elevated

6 Carcinoma with metastases to the bone. Occasional instances of hyperplasia of the parathyroids<sup>38</sup> and hypercalcemia, possibly due to hyperfunction of a metastasis to the parathyroids<sup>39</sup> have been noted. The serum phosphatase activity is discussed later

7 Renal rickets. This disease is commonly associated with hyperplasia of the parathyroids<sup>40</sup>. Disturbances in the growth of the long

31 Hamilton, B., and Schwartz, C. Rickets and Hyperparathyroidism, *Am J Dis Child* **46** 775 (Oct.) 1933

32 (a) Kay, H. D. Phosphatase in Growth and Disease of Bone, *Physiol Rev* **12** 384, 1932. (b) Smith, J., and Maizels, M. The Plasma Phosphatase in Rickets and Scurvy, *Arch Dis Childhood* **7** 149, 1932. (c) Bodansky, A., and Jaffe, H. L. Phosphatase Studies. III Serum Phosphatase in Diseases of the Bone. Interpretations and Significance, *Arch Int Med* **54** 88 (July) 1934, (d) footnote 6

33 Hunter and Turnbull<sup>19</sup>. Bodansky and Jaffe<sup>32c</sup>

34 Dietrich, A. Vergleichende Untersuchungen über Chondrodystrophie und Osteogenesis Imperfecta, *Jahrb d in- u ausland ges Med* **322** 122, 1915. Bauer, K. H. Ueber Osteogenesis imperfecta, *Deutsche Ztschr f Chir* **154** 166, 1920

35 Hunter, D. The Significance to Clinical Medicine of Studies in Calcium and Phosphorus Metabolism, *Lancet* **1** 999, 1930. Kay,<sup>32a</sup> and Bodansky and Jaffe<sup>32c</sup>

36 Ballin, M. Parathyroidism, *Ann Surg* **96** 649, 1932

37 Bulger, H. A., Dixon, H. H., Barr, D. P., and Schregardus, O. The Functional Pathology of Hyperparathyroidism, *J Clin Investigation* **9** 143, 1930

38 Klemperer, P. Parathyroid Hyperplasia and Bone Destruction in Generalized Carcinomatosis, *Surg, Gynec & Obst* **36** 11, 1923

39 Mason, R. L., and Warren, S. Metastatic Carcinoma Simulating Hyperparathyroidism, *Am J Path* **7** 415, 1931

40 Langmead, F. S., and Orr, J. W. Renal Rickets Associated with Parathyroid Hyperplasia, *Arch Dis Childhood* **8** 265, 1933

bones, osteoporosis and granular mottling of the skull are revealed by roentgenogram <sup>41</sup> The blood phosphatase activity is increased <sup>42</sup>

8 Chronic nephritis There is occasional association with compensatory (?) enlargement of the parathyroids <sup>43</sup> The blood phosphatase activity is normal <sup>44</sup> or slightly elevated, <sup>32a</sup> unless changes in the bone are present, as in cases of renal rickets

9 Nephrolithiasis Association with hypercalcemia and diffuse parathyroid hyperplasia occurs in some cases, without demonstrable changes in the bone <sup>10</sup> These instances are believed to represent a separate disease entity caused by excess of a parathyrotropic substance <sup>45</sup> demonstrable in the urine <sup>46</sup> The blood phosphatase activity in this interesting group is within normal limits <sup>47</sup>

10 Pituitary basophilism The occasional association of this disease with parathyroid hyperplasia <sup>48</sup> and osteoporosis <sup>49</sup> and the parathyrotropic activity of preparations of the anterior lobe of the pituitary gland <sup>48</sup> have been considered evidence of "secondary" hyperparathyroidism The blood phosphatase activity appears to be essentially normal in cases of pituitary basophilism <sup>50</sup>

With the possible exception of certain cases of impairment of renal function, the enlargement of the parathyroid glands noted in association

41 (a) Hamperl, H, and Wallis, K Ueber "renale Rachitis" und "renalen Zwergwuchs," *Virchows Arch f Path Anat* **288** 119, 1933 (b) Vogt, E C Renal Rickets, *Am J Roentgenol* **30** 624, 1933 (c) Langmead and Orr <sup>40</sup>

42 Kay <sup>32a</sup> Hunter <sup>35</sup> Vogt <sup>41b</sup>

43 Bergstrand, H Parathyroideastudien II Ueber Tumoren und hyperplastische Zustände der Nebenschilddrüsen, *Acta med Scandinav* **54** 539, 1921 Radnai, P Untersuchung der Nebenschilddrüsen bei Nierenkranken, *Frankfurt Ztschr f Path* **46** 97, 1933 Pappenheimer, A M, and Wilens, S L Enlargement of the Parathyroid Glands in Renal Disease, *Am J Path* **11** 73, 1935

44 Gutman and Gutman <sup>5c</sup> Kay <sup>32a</sup>

45 Albright, F, Churchill, E D, and Castleman, B Hyperparathyroidism Due to a Diffuse Hyperplasia of All Parathyroid Glands Rather Than to a Parathyroid Adenoma of One Gland, *J Clin Investigation* **13** 685, 1934

46 Hertz, S Demonstration of a Parathyreotropic Substance in Increased Amounts in the Urine of Patients with Hyperparathyroidism Due to Diffuse Hyperplasia of All Parathyroid Glands, *J Clin Investigation* **13** 698, 1934

47 Albright, Aub and Bauer <sup>10</sup> Castleman and Mallory <sup>25</sup>

48 Hertz, S, and Kranes, A Parathyreotropic Action of the Anterior Pituitary Histologic Evidence in the Rabbit, *Endocrinology* **18** 350, 1934

49 Cushing, H The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations, *Bull Johns Hopkins Hosp* **50** 137, 1932

50 Hare, D C Two Cases of Dyspituitarism (Case 1), *Proc Roy Soc Med* **27** 1017, 1934 Macbeth, A, and Simpson, S L Two Cases Demonstrating the Adrenogenital Syndrome, *ibid*, p 404 Gutman and Gutman <sup>5c</sup>



with the aforementioned heterogeneous group of diseases appears to be not autonomous but in the nature of a compensatory hyperplasia secondary to pathologic changes elsewhere. As most observers cited have pointed out, this does not necessarily imply overcompensation with the liberation of excessive parathyroid secretion sufficient to produce what might properly be called a state of hyperparathyroidism. When enlargement of the parathyroids and hypercalcemia coexist, as in cases of the nephrolithiasis syndrome described by Albright, Aub and Bauer,<sup>10</sup> the assumption of a state of hyperparathyroidism seems justified. But for the most part, the indicated morphologic changes in the parathyroid glands are not associated with hypercalcemia, hypophosphatemia or hypercalciuria—evidence of hyperparathyroidism which one expects except when marked renal insufficiency is present. Large, nonmalignant tumors of the parathyroids without evidence of parathyroid hyperfunction so far as skeletal changes are concerned have been described repeatedly. They appear to be analogous to nontoxic adenomas of the thyroid.

Similarly, hypercalcemia such as occurs frequently in cases of multiple myeloma and occasionally in instances of metastatic malignant growths in the bones does not, we believe, necessarily imply increased parathyroid activity but may well be due to rapid dissolution of bone resulting from malignant growth. With the exceptions already noted postmortem examination has revealed apparently normal parathyroid glands in such instances (case of J. M. for example).

Not can the increased blood phosphatase activity noted in some of the aforementioned conditions be construed as necessarily indicating parathyroid hyperfunction. The available evidence, to be presented later in the paper, suggests that the level of phosphatase in the blood is not a direct index of the degree of parathyroid activity.

#### PAGET'S DISEASE

Analyses of the blood were made in 76 cases of Paget's disease. This series includes instances of stages of the disease varying from the earliest demonstrable changes in the bone to the most severe and widespread skeletal involvement<sup>51</sup>. The cases are divided arbitrarily into four groups according to the extent of involvement of the bone, as indicated by roentgenographic examination of the skeleton. Many cases have been studied sufficiently long roentgenologically and clinically to appraise the activity of the lesions present in the bones. The results are shown in the following tabulation in which the bones involved by advanced lesions are indicated by bold face type.

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51 These cases are included in a clinical and roentgenologic study of Paget's disease (Gutman, A. B., and Kasabach, H. Paget's Disease [Osteitis Deformans]. Analysis of 116 Cases, *Am J M Sc*, to be published).

Number	Patient	Sex	Age, Years	Serum Calcium, Mg per 100 Cc	Serum Inorganic Phosphorus, Mg per 100 Cc	Serum Phosphatase, Bodansky Units per 100 Cc	Serum Nonprotein Nitrogen, Mg per 100 Cc	Bones Involved	Major Clinical Symptoms	Approximate Duration of Symptoms, Years
Group 1 Cases of Advanced, Widespread Paget's Disease										
1	F B	M	66	10.4	3.4	130.3	46	Skull, pelvis, humeri, femur, entire spine	Deformities, gait, pain	10
2	M B	M	38	10.6	3.6	111.7	35	Skull, spine, pelvis, femurs, tibiae, scapulas, clavicles, humerus, fibula	Deformities, gait, fracture	12
3	W M	M	65	9.7	3.3	109.9	34	Skull, spine, pelvis, femurs, humerus, ribs, scapula, clavicle	Deformities, gait, vision	15
4	A O	F	60	10.1	3.5	91.9	44	Skull, pelvis, femur, tibia, humerus, spine	Gait, fracture, pain	6
5	M S	F	64	10.4	3.4	59.5	39	Skull, pelvis, spine, tibia, femurs, humeri	Deformities, gait, paranoia	20
Group 2 Cases of Advanced Paget's Disease										
6	L M	M	51	10.7	3.2	122.2	32	Skull, pelvis, femurs, humeri, scapulas, spine, clavicle	Gait, pain, deformities	10
7	J R	F	54	10.6	3.7	117.5	28	Skull, femurs, spine, pelvis, humerus	Gait, pain, vision	10
8	C H	F	47	10.0	3.8	109.5	32	Skull, spine, pelvis, one rib	Pain	2
9	J W	M	64	10.7	3.7	94.3	36	Pelvis, femurs, skull, tibia, spine, humeri, scapulas	Pain, deformities	5
10	E M	F	50		4.2	92.8	30	Skull, pelvis, femurs	Deafness, deformities	5
11	F B	F	55	9.8	3.9	89.9	27	Skull, pelvis, femur	Pain, limp	4
12	H J	F	65	10.1	3.3	78.4	28	Skull, pelvis, femurs, spine, scapula	Deformity, gait	20
13	F F	M	69	11.0	3.2	77.6	37	Skull, pelvis, spine, femurs	Deafness, limp, deformities	7
14	E T	M	48	11.3	3.9	77.0	31	Skull, pelvis, tibia, femur	Pain, gait, deformities	10
15	M H	M	69	10.2	3.4	65.4	37	Pelvis, spine, femurs, skull	Pain, deformities	8
16	S C	F	45	11.5	2.9	63.9	35	Skull, femur, fibula	Fracture, pain	6
17	A C	M	59	10.7	3.8	62.9	46	Spine, pelvis, humeri, skull, tibia, clavicles, ulnas	Fracture, pain, deformity	9
18	M L	F	70	10.5	3.4	60.4	52	Skull, pelvis, humerus, femurs, tibia, tarsus, clavicles	Gait, asthenia, fracture	12
19	E S	F	37	9.8	3.6	57.9	25	Pelvis, spine, skull, scapulas	Asymptomatic	
20	R P	M	53	9.7	3.4	57.9	35	Pelvis, spine, femurs, humerus, clavicles, ribs, scapula, skull	Deformities	6
21	H S	M	50	10.3	3.7	55.0	37	Skull, pelvis, femur	Headache, pain, gait	12
22	N R	F	45	9.3	3.6	51.4	29	Skull, pelvis, tibia, spine, femurs, humeri, clavicle	Deformity, pain, deaf	5
23	E R	F	63	10.0	2.9	46.8	30	Skull, tibia, pelvis	Pain, deformity	7
24	W F	M	43	10.8	3.5	45.7		Pelvis, femur, skull	Pain	2
25	J S	M	54	10.8	3.8	45.2	24	Skull, pelvis	Deformity, pain	8
26	J M	M	57	10.2	2.7	44.4	36	Spine, pelvis, humerus, femurs, scapulas	Pain	4
27	A T	F	70		3.8	40.1	44	Pelvis, spine, skull, femurs	Pain	5
28	J S	F	60	10.6	3.7	38.4	38	Skull, femurs, spine, pelvis	Deformities	10
29	T M	M	64	10.4	3.8	38.2	38	Skull, tibia, ribs, scapulas	Deformities	6
30	M G	F	63	9.6	4.5	38.2	34	Skull, spine, pelvis, radius, ulna, femur, humerus	Deformities, gait	12
31	S S	F	62	10.1	3.7	37.9	33	Skull, spine, pelvis, femurs	Pain, headache	3
32	J L	F	55	11.5	3.3	37.7		Pelvis, skull, femur	Deformity, limp, pain	10
33	H N	M	69	10.1	4.1	36.9	40	Humerus, spine, pelvis, skull, scapula	Pain, deformity	7
34	I W	F	58	10.1	3.8	36.5	36	Spine, pelvis, tibia, skull, femurs, humerus, scapulas	Pain, deformities	8

Number	Patient	Sex	Age, Years	Serum Calcium, Mg per 100 Cc	Serum Inorganic Phosphorus, Mg per 100 Cc	Serum Phosphatase, Bodansky Units per 100 Cc	Serum Nonprotein Nitrogen, Mg per 100 Cc	Bones Involved	Major Clinical Symptoms	Approximate Duration of Symptoms, Years
35	M S	F	54	10.2	3.8	34.6	32	Tibias, pelvis, femur, skull, metacarpal	Deformities, gait, pain	8
36	S L	M	74	10.1	3.4	34.3	37	Skull, femurs, tibias	Deformities, gait	10
37	F R	M	59	9.9	3.5	33.7	36	Pelvis, femurs, skull, spine, tibia, humerus, scapulas, clavicle	Pain, deformity	5
38	H K	M	64	11.5	3.2	32.5	31	Pelvis, skull, spine, scapula	Deformities, gait	8
39	H B	F	74	10.5	3.2	32.1	32	Pelvis, tibias, femurs, skull	Pain, deformity, gait	24
40	B D	M	63	9.0	4.0	31.1	32	Pelvis, skull, femurs	Asymptomatic	
41	W O	M	51	10.7	3.0	30.9	30	Pelvis, spine, humerus, skull, femurs, scapula	Fracture	½
42	A L	F	63	10.1	5.1	29.4	42	Tibias, femurs, pelvis, skull, spine	Fracture, gait, deformities	2
43	G L	M	72	9.8	3.2	26.7	28	Pelvis, femurs	Pain	
44	L A	F	56	11.5	3.7	26.1	34	Tibia, humerus, skull	Fracture, gait, pain	9
45	M S	F	75	9.8	3.0	24.2	30	Pelvis, femurs, spine, scapula	Asymptomatic	
46	H S	F	55	10.7	3.2	23.0	36	Pelvis, femur, spine	Pain	3
47	J S	M	59	10.8	3.6	23.0	29	Pelvis, spine, skull, femurs	Deaf	5
48	J K	M	63	11.2	3.2	19.7	38	Skull, pelvis, spine, femur, humerus	Dizzy spells	3
49	J L	F	58	11.1	3.6	16.8	34	Femur, pelvis, sacrum	Deformities, gait, headache	12
50	D L	M	78	10.5	2.8	15.0	27	Pelvis, spine, femurs, skull, scapulas, humeri	Gait	10
51	R N	M	76	9.9	3.4	9.7	32	Femurs, pelvis, sacrum	Fracture, deformity	2
Group 3 Cases of Moderately Advanced Paget's Disease in One Area, in Most Instances with Early Lesions Elsewhere										
52	E F	F	62	9.2	3.2	53.6	37	Skull	Deformity, deaf	10
53	M D	F	58	10.1	2.5	49.1	33	Skull	Deformity	12
54	A T	F	43	10.4	3.4	20.8	30	Skull	Deformity	4
55	M B	F	54	10.9	3.3	13.8	35	Skull, humerus	Asymptomatic	
56	J S	M	56	10.3	3.7	13.6		Femur	Pain, limp	5
57	J T	F	73	10.6	3.7	13.5	28	Pelvis, lumbar vertebrae	Asymptomatic	
58	S H	M	45	10.6	3.2	13.1	30	Ilium, ischium, pubic bone on right side	Pain	¾
59	J H	F	55	9.9	3.5	12.2	32	Radius, sacrum, ilium	Deformity	5
60	A R	M	60	10.1	3.2	11.0	55	Humerus, ulna, pelvis	Fracture, pain	4
61	E C	F	77	9.6	3.1	9.1	26	Pelvis, skull	Asymptomatic	
62	C B	F	32	10.7	3.2	8.5	26	Skull, ischium, femur	Pain	3
63	H H	M	57	10.6	3.4	8.0	38	Pelvis, sacrum, femur	Headache	2
64	S F	M	65	10.3	3.4	7.6	27	Pelvis, femur, skull	Pain	½
65	C P	F	52	10.7	4.7	7.3	54	Humerus, femur, ilium	Asymptomatic	
66	M H	M	69	10.6	4.1	4.1	27	Pelvis	Asymptomatic	
Group 4 Cases of Early Localized Paget's Disease										
67	E M	M	56	17.2	3.8	8.3	47	Femur	See text	
68	L P	F	55	11.1	3.0	7.9	56	Ischium, pubic bone on right side	Pain, gait	4
69	S S	M	48	10.4	2.8	7.5	35	Sacrum	Pain	1
70	E G	F	34	9.8	2.9	6.9	26	Ischium, pubic bone on right side	Asymptomatic	
71	W J	M	54	9.4	2.8	5.7	30	Pelvis	Asymptomatic	
72	T M	M	72	10.1	3.2	5.2	39	Pubic bone, ischium on right side	Asymptomatic	
73	A S	M	49	8.7	3.3	5.0		Skull	Asymptomatic	
74	W W	M	75	9.9	3.5	4.9	51	Skull	Asymptomatic	
75	W B	M	70	9.5	3.0	4.5	31	Skull	Asymptomatic	
76	E L	M	49	9.2	3.0	1.8	28	Ischium on right side	Asymptomatic	

*Serum Calcium*—Values within the normal range of from 9 to 11 mg per hundred cubic centimeters were found in 65 of the 74 cases in this series, exceeding 11.5 mg only in the following instance (case 67)

An American man, aged 57, was admitted to the Presbyterian Hospital on Feb 11, 1933, because of a loss of 45 pounds (20.4 Kg) in weight, increasing weakness, anorexia and vomiting for three and one-half months. He had had a dry, hacking cough for ten years, which for the preceding three months was associated with sharp pain in the right side of the chest and was intermittently productive of blood-tinged sputum. Roentgenographic examination of the chest disclosed a large cavity, with a level of fluid, in the upper lobe of the right lung. It was believed that this was an abscess of the lung, the suppuration probably being secondary to a bronchogenic carcinoma. Roentgenographic examination of

TABLE 2—*Summary of Studies of the Blood in a Case (E. M.) of Bronchogenic Carcinoma with Incidental Localized Paget's Disease and Unexplained Hypercalcemia*

Date	Serum					
	Calcium, Mg per 100 Cc	Inorganic Phos- phorus, Mg per 700 Cc	Phos- phatase, Bodansky Units per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc	Protein, per Cent	Carbon Dioxide, Volume per Cent
7/ 6/33	13.5	2.1		28	4.9	59
7/10/33	13.9	2.4	6.5	22	5.0	63
8/ 3/33	17.2	3.8	8.3	47	5.5	
8/16/33	18.9	4.5	10.9	40	5.7	
8/22/33	16.4	3.9	8.7	38	5.6	133.7

the skeleton failed to reveal metastases in the bones, but it disclosed localized Paget's disease involving the upper half of the right femur. This lesion was asymptomatic and was not suspected clinically. Loss of weight, weakness, anorexia, vomiting and intermittent fever continued, with only temporary amelioration after rib resection and drainage on July 12. Studies of the blood revealed marked hypercalcemia, the most striking of many peculiarities in the electrolytes of the serum (table 2). Roentgenograms of the entire skeleton on August 14 showed no evidence of hyperparathyroidism, multiple myeloma or metastatic malignant growth in the bones to account for the hypercalcemia. There was no apparent change in the area of Paget's disease in the right femur.

The course of the disease was progressively downward, terminating in death on August 25. Postmortem examination revealed an extensive bronchogenic carcinoma in the upper lobe of the right lung with considerable secondary suppuration. No metastases were noted. Sections of the ribs, calvarium and vertebrae were normal on histologic examination. A section from the greater trochanter of the right femur showed Paget's disease. The parathyroid glands appeared normal on gross and histologic examination. The kidneys showed a thin sub-

capsular zone of round cell infiltration, the tubules contained calcified bodies and many granular and cellular casts. The renal changes were interpreted as indicative of low grade interstitial nephritis.

It is believed that the hypercalcemia in this case was not due to the localized and relatively inactive Paget's disease but to complicating factors as yet wholly obscure.

*Serum Inorganic Phosphorus*—The values in this series were within the normal range for the method employed—2.7 to 4 mg per hundred cubic centimeters—except in 6 cases in which values of more than 4 mg were obtained, usually associated with high normal or definitely elevated values for the nonprotein nitrogen of the serum. In 1 instance the inorganic phosphorus content of the serum was 2.5 mg per hundred cubic centimeters.

*Phosphatase Activity of the Serum*—In 75 of the 76 cases studied the activity exceeded the normal maximum value of 4 Bodansky units. A value of 1.8 Bodansky units was found in case 76, in which involvement of bone was the least extensive in the entire series. In this case discrete areas of bony condensation in the body of the right ischium, not in relation to the hip joint, were believed to be the result of early localized Paget's disease.

Our results are in general agreement with those reported in several recent extensive studies. Kay, Simpson and Riddoch<sup>52</sup> found that the value for plasma phosphatase was increased in 25 cases of Paget's disease. Their values varied from 0.4 to more than 3 Kay units, the increase in phosphatase activity being roughly proportional to the extent of involvement of the bone. The calcium content of the serum and the amount of inorganic phosphorus in the plasma were within normal limits. Bodansky and Jaffe<sup>32c</sup> reported values for the serum phosphatase of from 4.9 to 23.1 Bodansky units in 13 cases of localized Paget's disease and of from 5.0 to 12.5 Bodansky units in 9 additional cases of advanced polyostotic Paget's disease. In a twenty-third case in their series, the serum phosphatase activity proved to be only 1.5 Bodansky units, although the skeleton was extensively involved. Pathologic examination disclosed that the widespread lesions were markedly sclerosed, typical of healed lesions of Paget's disease, with little evidence of activity. The calcium content of the serum in 14 of 15 cases in which examinations were made ranged from 9.2 to 10.8 mg per hundred cubic centimeters, and the inorganic phosphorus content in 22 of 23 cases, from 2.5 to 5 mg. In 1 case, classified roentgenologically as an instance of Paget's disease, the calcium content of the serum was 12.4

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<sup>52</sup> Kay, H. D., Simpson, S. L., and Riddoch, G. Osteitis Deformans, Arch Int Med **53** 208 (Feb.) 1934.

mg and the inorganic phosphorus content, 1.8 mg. O'Reilly and Race<sup>53</sup> found values for plasma phosphatase varying from 0.21 to 4.3 Kay units in 21 cases of Paget's disease, with the calcium content of the serum ranging from 9.1 to 11.3 and the inorganic phosphorus content of the plasma, from 2 to 3.95 mg. In 2 of these cases, in which the disease was presumed to be quiescent, the values for phosphatase were within the normal range. Roberts<sup>53</sup> made examinations in 13 cases and reported values for plasma phosphatase of from 6.5 to 32.1 Roberts units (the normal being about 4 units). Belden and Bernheim<sup>54</sup> reported the results of their determination of the calcium content of the serum in 6 cases as from 9.6 to 12.3 mg per hundred cubic centimeters. In 3 other instances the calcium content of the serum was described as normal and in a tenth case as low. Jerome and Compere<sup>55</sup> in 9 cases of Paget's disease found values for the calcium content of the serum between 8.97 and 11.5 mg, and for the inorganic phosphorus content between 2.4 and 5.7 mg. Hunter<sup>55</sup> in 7 cases reported values for the serum calcium of from 8.2 to 10.8 mg, for plasma phosphate, from 3 to 3.5 mg, and for plasma phosphatase, from 0.66 to more than 1.4 Kay units. Snapper<sup>56</sup> reported values for serum calcium of from 9.9 to 11.5 mg in 7 cases of Paget's disease, in 4 of which the amount of inorganic phosphorus was determined and found to vary from 2.6 to 3.4 mg.

In addition to these detailed reports, Albright, Aub and Bauer<sup>10</sup> referred to their results in more than 30 cases of Paget's disease, they stated that in only 1 instance did the disease seem to be complicated by hyperparathyroidism, i. e., to present hypercalcemia and hypophosphatemia. Phemister<sup>57</sup> remarked that in none of his 10 cases of Paget's disease was an elevation of the calcium content of the serum or a lowering of the amount of inorganic phosphorus shown. In addition to these studies, a number of isolated reports of cases of Paget's disease have appeared, which are summarized as follows (the text should be consulted for reports from the literature of more extensive series of cases [Kay,

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<sup>53</sup> Roberts, W. M. Variations in the Phosphatase Activity of the Blood in Disease, *Brit J Exper Path* **11** 90, 1930.

<sup>54</sup> Belden, H. W., and Bernheim, A. Clinical and Therapeutic Considerations of Osteitis Deformans, *Radiology* **18** 325, 1932.

<sup>55</sup> Jerome, J. T., and Compere, E. L. The Pathological and Biochemical Changes in Paget's Disease, *Illinois M J* **64** 449, 1933.

<sup>56</sup> Snapper, I. Maladie osseuses et parathyroïdes, *Ann de méd* **29** 201, 1931.

<sup>57</sup> Phemister, D. B., in discussion on Ballin<sup>36</sup>

Simpson and Riddoch, <sup>52</sup> Bodansky and Jaffe, <sup>52c</sup> O'Reilly and Race, <sup>5b</sup> Roberts, <sup>53</sup> Belden and Bernheim, <sup>54</sup> Jerome and Compere, <sup>55</sup> Hunter, <sup>55</sup> Snapper, <sup>56</sup> Albright, Aub and Bauer, <sup>10</sup> and Phemister <sup>57</sup>])

Year	Author	Patient	Sex	Age, Years	Blood		Bones Involved	Comment
					Cal cium, Mg per 100 Cc	Inor ganic Phos phorus, Mg per 100 Cc		
1924	Koechig <sup>58</sup>				12.1 11.8		Not specified Not specified	Calcium determined by Lyman's method
1924	Schoen <sup>59</sup>		F	29	15.2		Skull, tibia, femur	
1927	Cuthbertson <sup>60</sup>				11.4		Skull, bones of legs, ulna	
1927	Van Hazel and Andrews <sup>61</sup>	J	F	63	13.1 8.7		Tibia	
1928	Barrenscheen and Gold <sup>62</sup>	N S H			13.8 13.8 11.4		Tibia Femurs Humerus with sarcoma	Calcium determined by de Waard's method
		H			11.2		Polyostotic	
1931	Garvey <sup>63</sup>	S	M	57	10.1		Skull, pelvis, spine, femurs	
1931	Lasch <sup>64</sup>	G E	M M	75 67	12.0 12.2	3.9 4.1	Skull, tibia Skull, bones of arms and legs	Calcium determined by de Waard's method
		M K M	F F M	68 56 61	11.6 10.2 11.2	4.0 3.9 4.0	Tibia Skull Skull	
1931	Weltj <sup>65</sup>				"Normal"		Not specified	
1932	Berman <sup>66</sup>	2 3	F M	52 58	11.8 11.5	3.2 3.9	Skull, legs Skull, spine, tibiae, pelvis	
		4	M	48	10.8	4.5	Skull, tibiae	
1932	Jung and Hakki <sup>67</sup>	C O		56 58	8.8 8.2		Not specified Not specified	Calcium determined by Hirth's method

58 Koechig, I. Calcium Content of the Blood in Pathologic Conditions, *J Lab & Clin Med* **9** 679, 1924

59 Schoen, R. Ostitis deformans (Paget) mit Diabetes insipidus, nervosen und endokrinen Storungen, *Munchen med Wchnschr* **71** 1713, 1924

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61 Van Hazel, W., and Andrews, E. Osteitis Deformans, *Surg, Gynec & Obst* **45** 54, 1927

62 Barrenscheen, H. K., and Gold, E. Kalkuntersuchungen bei Skeletterkrankungen, *Wien med Wchnschr* **78** 1340, 1928

63 Garvey, P. H. A Case of Paget's Disease (Osteitis Deformans) Complicated by Tumor of the Nasopharynx with Involvement of Cranial Nerves and the Gasserian Ganglion, *J Nerv & Ment Dis* **73** 395, 1931

64 Lasch, F. Biochemische Untersuchungen bei Ostitis deformans Paget, *Wien Arch f inn Med* **21** 159, 1931

65 Weltj, M. H. Du rôle de l'hyperparathyroïdisme dans certaines dystrophies osseuses et dans la polyarthrite ankylosante, *J de chir* **38** 633, 1931

66 Berman, L. The Endocrine Treatment of Paget's Disease, *Endocrinology* **16** 109, 1932

67 Jung, A., and Chmassi, H. A. Etudes sur la calcémie, *Rev de chir Paris* **51** 537, 1932

Year	Author	Patient	Sex	Age, Years	Blood		Bones Involved	Comment
					Cal- cium, Mg per 100 Cc	Inor- ganic Phos- phorus, Mg per 100 Cc		
1932	Kasabach and Dyke <sup>68</sup>	W	F	54	13 16	4 0	Spine, humeri, pelvis, femurs, tibia	Calcium normal in 1934
		K	M	59	11 13		Pelvis, spine, femurs, scapulas, humeri	
		P	M	33	"Normal"		Skull, tibia (osteoporosis circumscripta)	
1932	Kienbock and Sereghy <sup>69</sup>	R	M	64	18 0		Generalized	Method for calcium?
1932	Labbe et al <sup>70</sup>	V			9 7	4 0	Not specified	
		C			8 8	2 7	Not specified	
		D			11 4	4 8	Not specified	
1932	Laederich et al <sup>71</sup>	C	M	69	9 6	3 9	Skull, humerus, tibia, ribs, phalanges, clavicles	
1932	Laignel Lavastine and Boquien <sup>72</sup>	M	F	72	9 5	10 5	Generalized	
1932	Langeron et al <sup>73</sup>	1	M	54	9 5	3 2	Tibias, spine, pelvis, clavicles	
		2	M	41	8 6		Skull, femurs, spine	
1932	Martin and Sarasin <sup>74</sup>	H	M	75	10 2	11 4	Pelvis, skull, femurs	
1932	Rabinowitch <sup>75</sup>	I	M	42	9 2	3 8	Femurs, humerus, rib	
1932	Santoro <sup>76</sup>	D	F	56	14 0		Skull, pelvis, tibias	Method for calcium?
1932	Schrijver <sup>77</sup>	W	M	82	9 6		Skull, tibia	
		M	M	67	9 0		Skull	
1932	Schulmann and Meillaud <sup>78</sup>	D	F	80	8 8		Skull	

68 Kasabach, H. H., and Dyke, C. G. Osteoporosis Circumscripta of the Skull as a Form of Osteitis Deformans, *Am J Roentgenol* **28** 192, 1932

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72 Laignel-Lavastine, M., and Boquien, Y. Sur un cas de maladie de Paget, *Bull et mém Soc med de hôp de Paris* **48** 685, 1932

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75 Rabinowitch, I. M. Metabolic Studies in a Case of Osteitis Deformans, *J Nutrition* **5** 325, 1932

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77 Schrijver, D. Ostitis deformans (Paget) und Psychose, *Ztschr f d ges Neurol u Psychiat* **141** 645, 1932

78 Schulmann, E., and Meillaud, P. Un cas de maladie osseuse de Paget à détermination uniquement crânienne, *Bull et mém Soc d hôp de Paris* **48** 1178, 1932



Year	Author	Patient	Sex	Age, Years	Blood		Bones Involved	Comment
					Cal cium, Mg per 100 Cc	Inor ganic Phos phorus, Mg per 100 Cc		
1933	Bachmann <sup>79</sup>	H		56	10.8		Spine, pelvis, femurs	
		I		48	11.0		Spine, femurs	
		J		47	10.6		Skull, spine, pelvis	
1933	Colt and Lvall <sup>80</sup>	1	F	54	9.8	4.5	Skull, pelvis, tibia, rib	Phosphatase, 3.96 units
1933	Benjamin and Hess <sup>81</sup>			60	10.7	4.7	Not specified	
1933	Korner <sup>82</sup>	1	M	57	11.3		Skull, pelvis, ribs, bones of legs	
1933	Labbe and Petresco <sup>83</sup>	C	F	65	8.8	2.7	Generalized	
1933	Stauder <sup>84</sup>	I	M	56	10.0		Skull, pelvis, humeri	
1933	van Bogaert <sup>85</sup>	T	M		10.2	3.7	Skull, tibiae, femurs, spine	
		M	M		9.0		Pelvis, femurs	
1934	Arnulf and van der Linden <sup>86</sup>	I	M	63	9.0		Femur, pelvis, spine	
1934	Barth <sup>87</sup>	1	M	59	10.0		Skull, pelvis, lumbar vertebrae	
1934	Gouterman <sup>88</sup>	M	M	65	18.0	3.7	Skull, pelvis (femurs?)	Method for calcium?
1934	Haguenau et al <sup>89</sup>	M	M	62	14.2		"Diffuse"	Method for calcium?
1934	Levin <sup>90</sup>	A	M	63	12.0		Skull, humerus, femurs, pelvis	

79 Bachmann Ein Beitrag zur Ostitis deformans Paget, Rontgenpraxis 5 161, 1933

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85 van Bogaert, L. Ueber eine hereditare und familiare Form des Paget-schen Ostitis deformans mit Chorioretinitis pigmentosa, Ztschr f d ges Neurol u Psychiat 147 327, 1933

86 Arnulf, G., and van der Linden. Apropos des fractures dans la maladie de Paget, Rev de chir, Paris 53 279, 1934

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88 Gouterman, J. I. Ocular Complications in Paget's Disease, Am J Ophth 17 334, 1934

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90 Levin, I. A Comparative Analysis Between the Pathogenesis of Osteodystrophies and Bone Tumors, Radiology 22 266, 1934

Year	Author	Patient	Sex	Age, Years	Blood		Bones Involved	Comment
					Calcium, Mg per 100 Cc	Inorganic Phosphorus, Mg per 100 Cc		
1934	Meyer <sup>91</sup>	I	M	46	9.6	3.3	Spine, pelvis, femurs, skull, humeri, tibiae, radii	
1934	Rummert <sup>92</sup>	K	M	31	10.2	11.4		
1934	Scriver and Venning <sup>93</sup>	K	F	64	10.8	3.1	Skull, spine, femurs	
		A	F	47	9.5	3.9	Skull, spine, femurs, tibiae, fibulae, humerus	
		D	M	62	8.6	3.7	Skull, pelvis, tibiae, femur	
		T	F	53	6.9	8.3	Skull, tibiae, fibulae, femurs, spine	
1934	von Bonsdorff <sup>94</sup>		F	59	11.1	12.0	Tibiae, skull, spine, humeri	
1934	Weibel <sup>95</sup>		F	57	8.9	1.5	Skull, spine	
1935	Robbins and Kydd <sup>96</sup>	4	M	64	10.2	7.6	Spine, pelvis, femur, skull, clavicle	

### MULTIPLE MYELOMA

The results of analyses of the blood in 6 cases of multiple myeloma are summarized in table 3. In cases 1 and 2 the diagnosis was confirmed by postmortem examination, which in both instances revealed widespread lesions of the plasma cell type. Biopsy or autopsy was not permitted in cases 3 to 6. The diagnosis in these instances rests on the roentgenographic finding of multiple lesions of the bones, characteristic both as to appearance and localization, a typical clinical history and course and consistent laboratory findings. In each instance extensive investigation failed to reveal evidence of a primary neoplasm involving organs from which metastasis commonly takes place to the bones. The possibility of metastatic lesions from an unrecognized focus cannot be ruled out, however.

The amount of serum calcium was definitely elevated in 4 of the 6 cases in this series. In case 1 the level of the serum calcium was normal at the first examination, but it gradually rose. In case 2 the calcium

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95 Weibel, W. Ueber Ostitis deformans (Paget) des Schädels mit Horstörungen, *Schweiz. med. Wchnschr.* **15** 430, 1934.

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TABLE 3—Summary of Studies of the Blood in 6 Cases of Multiple Myeloma

Number	Patient	Sex	Age, Years	Date	Serum			Urine	Roentgenographic Findings	Relevant Clinical Data
					Calcium, Mg per 100 Cc	Inorganic Phos- phorus, Mg per 100 Cc	Phos- phatase, protein BodanskyNitrogen, Units per Mg per 100 Cc	Protein, per Cent		
1	J M	M	64	1/24/34	10.5	3.7	1.7	48		
				2/6/34	12.0				Multiple areas of de- struction of bone in ribs, lumbar and tho- racic vertebrae, pelvis, femurs and scapula	Pain in back, shoulders and arm, loss of 30 lbs., pallor, tenderness over thoracic verte- brae, terminal fever, hemo- globin, 65% red cells, 3,100,000, death, 2/26/34, parathyroids normal
				2/27/34*	15.3					
2	A S	F	58	5/8/34†						
				5/17/34	8.5	2.6	5.2	40	Multiple areas of de- struction of bone in spine, ribs, skull, pelvis, upper half of humeri and femurs	Loss of weight, pain in chest and back, pallor, cachexia, pallor and weakness, hemoglobin, 45%, red cells, 1,800,000, death, 7/5/34
3	D F	M	60	10/24/32	15.5	3.0		Urea 30		
				11/1/32†	16.1	3.9	4.0		Multiple areas of decreased density in skull, ribs, radius, ulna and spine	Pallor, weakness, loss of 25 lbs., pathologic fractures of ribs and humerus, dyspnea, hemo- globin, 33%, red cells, 1,300,000, death, 4/12/33
4	P F	M	59	10/25/33	15.7	1.9				
				10/29/33	17.0	1.8	3.0	125	Multiple areas of decreased density in ribs, clavicles, cervical and thoracic verte- brae and scapulae, one punched out area in femur	Pain in chest, tenderness over lumbar spine, frequency of urination, uremia, auricular fibrillation, slightly enlarged, soft nonnodular prostate, terminal fever, hemoglobin, 89%, red cells, 4,200,000, death, 10/31/33
5	M O	F	56	4/20/33#	"Normal"	3.0	5.0	15	Multiple punched out areas in skull, spine, ribs and long bones	Pain, loss of weight, patho- logic fractures, anemia, death, December 1933
6	A C	M	47	2/21/34	13.3	6.0	4.0	80	Multiple punched out areas in ribs, scapula, pelvis and humeri	Pain in chest and neck, tender- ness over ribs and spine, loss of 20 lbs., low grade fever, hemoglobin, 78%, red cells, 4,380,000, death, 4/12/34
				3/1/34	13.0	3.5	5.3	65		

\* The blood was obtained eighteen hours after death

† This case occurred in the service of Dr. M. Lentz

‡ Dr. A. Bodansky determined the values in this case

# This case occurred in the service of Dr. Rolfe Long

content of the serum was maintained at normal levels for several years, but decreased to 8.5 mg per hundred cubic centimeters in the terminal stages of the disease. In the only examination of the blood made in case 5 the amount of serum calcium was normal. Essentially normal values for the amount of inorganic phosphorus in the serum were obtained, except when impairment of renal function caused an increase. The serum phosphatase activity varied from 1.7 to 5.3 Bodansky units. In cases 2, 3, 5 and 6 the value for serum phosphatase slightly exceeded the normal maximum, but in view of the extensive involvement of bone the increase was insignificant compared with values found in cases of advanced hyperparathyroidism. The protein content of the serum was somewhat increased in cases 1, 4 and 5, but it was normal in cases 3 and 6 and low in case 2. The frequent occurrence of hypercalcemia, the normal or slightly increased amount of inorganic phosphorus and phosphatase in the blood and the irregular occurrence of hyperproteinemia observed in the cases in our series are representative of the reports in the literature, a summary of which follows:

Year	Authors	Patient	Sex	Age, Yrs	Serum			Evidence for Diagnosis
					Cal-cium, Mg per 100 Cc	Inorganic Phos-phorus, Mg per 100 Cc	Pro-tein, Per-centage	
1923	Briggs <sup>97</sup>				10.0	4.0		
1927	Charlton <sup>98</sup>		F	57	12.0	16.0		Autopsy
1927	Currie <sup>99</sup>	S	M	59	10.0			Bence Jones protein
1928	Belden <sup>100</sup>	14	F	57	15.3	18.7	2.7	3.7
1928	Durman <sup>101</sup>		M	31	16.1	3.4	4.1	Autopsy
1928	Perlzweig et al <sup>102</sup>	E	M	40	10.8	4.8	12.3	13.8
1929	Hewitt <sup>103</sup>	1	M	46	12.8		6.3	Bence Jones protein
		2	F	66	9.4			Bence Jones protein
		5	M	59	9.7			Bence-Jones protein
1929	Ohlsson and Nordh <sup>104</sup>		M	37	15.0			Bence Jones protein
1929	Schittenhelm <sup>105</sup>		F	46	20.0	10.4		

97 Briggs, A. P. A Study of the Inorganic Elements of Blood Plasma, *J Biol Chem* **57** 351, 1923

98 Charlton, J. J. Multiple Myeloma, *Arch Int Med* **40** 98 (July) 1927

99 Currie, R. A. Case of Bence-Jones Proteinuria, with a Note on the Urinary Excretion of the Mineral Elements, *Glasgow M J* **25** 31, 1927

100 Belden, W. W. Bone Diseases, *Radiology* **11** 281, 1928

101 Durman, D. C. Myeloma of the Spine, *Ann Surg* **88** 975, 1928

102 Perlzweig, W. A., Delrue, G., and Geschickter, C. Hyperproteinemia Associated with Multiple Myelomas, *J A M A* **90** 755 (March 10) 1928

103 Hewitt, L. F. Urine Proteins in Nephrosis, Pregnancy and Myelomatosis, *Lancet* **1** 66, 1929

104 Ohlsson, E., and Nordh, G. Der Tryptophangehalt in Bence-Jones-Eiweiss, *Biochem Ztschr* **215** 440, 1929

105 Schittenhelm, A. Multiple Myelom (Kahlersche Krankheit), *Deutsche med Wchnschr* **55** 508, 1929

Year	Authors	Patient	Sex	Age, Yrs	Serum			Evidence for Diagnosis
					Calcium, Mg per 100 Cc	Inorganic Phosphorus, Mg per 100 Cc	Protein, Per centage	
1930	Barr and Bulger <sup>106</sup>	3	F	46	16.0	17.8	3.7	Autopsy (patient at St Louis City Hospital)
1930	Perla and Hutner <sup>107</sup>	1	M	43	13.4	14.6	6.2	Autopsy
1930	Smith <sup>108</sup>							"Two cases with hypercalcemia"
1930	Soper and Stroud <sup>109</sup>							"One case with hypercalcemia"
1931	Center and Merar <sup>110</sup>		M	70	7.0			Bence Jones protein
1931	Jores <sup>111</sup>	1	M	57	12.4	15.4	4.1	Autopsy
		2	F	43	18.2	20.2	3.5-4.0	Bence Jones protein
1931	Snapper <sup>112</sup>	1			15.4	4.3		
		2			12.0	5.2		
		3			10.1	5.6		
		4			12.5	5.2		
		5			11.8	2.8		
1931	Turner <sup>113</sup>				13.2	3.4	6.56	
1932	Ask-Upmark <sup>114</sup>							"Normal calcium in several cases"
1932	Aub and Farquharson <sup>115</sup>	M	F	27	10.4	9.8	3.6	Biopsy
1932	Freund and Magnus Levy <sup>116</sup>	L	M	52	11.6		<6.0	Bence Jones protein
1932	Green <sup>117</sup>		M	48	"High"	"High"		
1932	Mainzer <sup>118</sup>		M	46	11.9	12.5	4.8	Autopsy
1932	Reimann <sup>119</sup>	N	M	46	18.0		10.1	Autopsy

106 Barr, D. P., and Bulger, H. A. The Clinical Syndrome of Hyperparathyroidism, *Am J M Sc* **179** 449, 1930

107 Perla, D., and Hutner, L. Nephrosis in Multiple Myeloma, *Am J Path* **6** 285, 1930

108 Smith, F., cited by Barr and Bulger<sup>106</sup>

109 Soper, H. W., and Stroud, C. M., cited by Bulger, Dixon, Barr and Schregardus<sup>37</sup>

110 Center, C. D., and Merar, T. J. Multiple Myeloma, *Illinois M J* **60** 286, 1931

111 Jores, A. Beitrag zur Differentialdiagnose des multiplen Myeloms und der Ostitis fibrosa generalisata, *Klin Wchnschr* **10** 2352, 1931

112 Snapper, I. Calcium and Inorganic Phosphates of the Serum in Hyperparathyroidism and Myeloma, *Acta brevia neerland* **1** 25, 1931

113 Turner, R. H. The Pathologic Physiology of Pellagra. III The Serum Calcium and Phosphorus, With Especial Reference to Nervous Symptoms, *J Clin Investigation* **10** 87, 1931

114 Ask-Upmark, E. Beitrag zur Differentialdiagnose des multiplen Myeloms und der Ostitis fibrosa generalisata, *Klin Wchnschr* **11** 288, 1932

115 Aub, J. C., and Farquharson, R. F. Studies of Calcium and Phosphorus Metabolism. XV In Various Metabolic and Bone Diseases, *J Clin Investigation* **11** 235, 1932

116 Freund, R., and Magnus-Levy, A. Multiple Myelome. V Ueber Besonderheiten der Blutzusammensetzung, *Ztschr f klin Med* **121** 1, 1932

117 Green, T. M. Multiple Myeloma, *South Med & Surg* **94** 513, 1932

118 Mainzer, F. Bence-Jonessche Proteinurie und Nierenfunktion, *Ztschr f klin Med* **119** 363, 1932

119 Reimann, H. A. Hyperproteinemia as a Cause of Autohemagglutination, *J A M A* **99** 1411 (Oct 22) 1932

Year	Authors	Patient	Sex	Age, Yrs	Serum			Evidence for Diagnosis
					Cal cium, Mg per 100 Cc	Inorganic Phos phorus, Mg per 100 Cc	Pro tein, Per centage	
1932	Shirer et al <sup>120</sup>	1	M	64	12 2 15 5	2 6 8 0	10 0 13 8	Phosphatase, 0 12 Kay units autopsy
		2	F	49	11 2	4 3	11 4 10 0	Bence Jones protein
1932	Slavens <sup>121</sup>		M	4	"Nor mal"	"Nor mal"		Biopsy (plasmocytoma ?)
1932	Wirth <sup>122</sup>	H	M	51	13 2	3 4	6 6	
1933	Bell <sup>123</sup>	81	M	59	10 9 15 8		5 9	Autopsy
		83	M	51	18 2		6 5	Autopsy
		86	M	52	"Normal"			Autopsy
1933	Bulger and Gaus mann <sup>124</sup> (Case 27,621)	S			13 5 18 1	6 8 6 2		
					16 5 16 9	4 0 4 9		
1933	Caylor and Nickel <sup>125</sup>		F	52	8 0 19 5	3 5 4 0		Biopsy
1933	Chester <sup>126</sup>	1	M	46	11 0	4 2	4 7	Autopsy
		2	F	55	"Normal"		4 7	Bence Jones protein
1933	Ellermann and Schröder <sup>127</sup>		M	42	10 8			
1933	Herbert <sup>128</sup>	Ho	F	54	16 9	4 2	12 6	Autopsy
		H	M	55	10 6	4 7	6 5	
1933	Langeron et al <sup>129</sup>	D	M	55	9 8			Biopsy
1933	Lenshoek <sup>130</sup>	2	M	61	11 8 12 2	3 7 4 7	8 3	Biopsy
1933	Magnus Levy <sup>131</sup>	D	M	56	10 6		6 5	Bence Jones protein
		F	F	64	8 6		7 3	Autopsy
		B	F	46	12 3		9 9	Autopsy
		P	F	50	11 9	3 2	13 0	Bence Jones protein
		H	M	64	13 3		12 0	Autopsy
		V <sub>1</sub>	F	59	11 0		13 6	Autopsy
		V <sub>2</sub>	M	59	15 9		10 0 12 1	Autopsy

120 Shirer, J W , Duncan, W , and Haden, R L Hyperproteinemia Due to Bence-Jones Protein in Myelomatosis, Arch Int Med **50** 829 (Dec ) 1932

121 Slavens, J J Multiple Myeloma in a Child Report of a Case, Proc Staff Meet , Mayo Clin **7** 687, 1932

122 Wirth, W R Multiple Myeloma Report of a Case, New Orleans M & S J **84** 698, 1932

123 Bell, E T Renal Lesions Associated with Multiple Myeloma, Am J Path **9** 393, 1933

124 Bulger, H A , and Gausmann, F Magnesium Metabolism in Hyperparathyroidism, J Clin Investigation **12** 1135, 1933

125 Caylor, H D , and Nickel, A C Multiple Myeloma Simulating Hyperparathyroidism, Ann Surg **97** 823, 1933

126 Chester, W Multiples Myelom und Hypoproteinämie, Ztschr f klin Med **124** 466, 1933

127 Ellermann, M , and Schröder, G E Et tilfaelde af myelom med epileptiforme kramper, Hospitalstid **76** 102, 1933

128 Herbert, F K The Total and Diffusible Calcium of Serum and the Calcium of Cerebrospinal Fluid in Human Cases of Hypocalcemia and Hypercalcemia, Biochem J **27** 1978, 1933

129 Langeron, L , Martin, J F , and Guichard, A Considerations anatomocliniques sur les myelomes multiples des os, Lyon méd **151** 709, 1933

130 Lenshoek, C H Over stoornissen in de stoffwisseling der mineralen bij ostitis fibrosa generalisata en bij multiple myelomen, Nederl tijdschr v geneesk **77** 1193, 1933

131 Magnus-Levy, A Multiple Myelome VII Euglobulinämie Zur Klinik und Pathologie Amyloidosis, Ztschr f klin Med **126** 62, 1933

Year	Authors	Patient	Sex	Age, Yrs	Serum			Evidence for Diagnosis
					Cal cium, Mg per 100 Cc	Inorganic Phos- phorus, Mg per 100 Cc	Pro- tein, Per centage	
1933	Rypins <sup>132</sup>	S	F	22	11.0	4.0		Autopsy
1933	Wintrobe and Buell <sup>133</sup>	R	F	56	"Nor- mal"	"Nor- mal"		Autopsy
1934	Albright et al. <sup>134a</sup>	M	F	50	"Normal", "Normal"			Phosphatase, 1 Bodansky unit
1934	Bodansky and Jaffe <sup>132c</sup>	10	M			3.1		Phosphatase, 4.8 Bodansky units
		11	F	60	13.2	4.0		Phosphatase, 1.8 Bodansky units
		12	M	40	16.1	3.4		Phosphatase, 4.9 Bodansky units (our case D F)
1934	Denker and Brock <sup>134</sup>	L	F	15	9.2, 9.8	3.2	42.5, 5	"Phosphatase increased biopsy
1934	Ehrstrom <sup>135</sup>	J	F	43	10.6, 9.2			Biopsy
1934	dalla Volta <sup>136</sup>	C	F	56	15.6, 16.0			Autopsy
1935	Cantarow <sup>137</sup>	P	F	41	12.9, 9.2	5.8, 6.8	87.1, 11.3	Autopsy
1935	Berglund, Medes et al. <sup>138</sup>	K H			13.0 13.6		7.0 17.6	Bence Jones protein Bence Jones protein
1935	Case records of Mass Gen Hosp Case 21,082	Gen M	Hosp	50	13.9	4.7	13.5, 11.7	Autopsy, phosphatase 3.4 units (Bodansky)
	Case 21,052 <sup>139</sup>		F	60	11.8, 12.9	4.7, 8.8		Autopsy
1935	Robbins and Kydd <sup>96</sup>	B C A	M M M	60 52 34	18.1, 11.3 11.3, 10.5 18.8, 10.3	5.7, 2.3 9.7, 4.7 6.6, 3.1	13.1, 9.8 6.8, 6.0 7.8, 6.4	Autopsy Biopsy Autopsy

#### NEOPLASTIC DISEASE OF THE BONES

The results of analyses of the blood in 39 cases of carcinoma with metastases to the bones and in 6 cases of primary sarcoma of the bone are summarized in the following tabulation. We have included only cases in which advanced lesions of the bone were unequivocally demonstrable by roentgenogram, and in which jaundice was not apparent clinically or on examination of the serum. The protein content of the

132 Rypins, E. L. An Unusual Roentgenologic Finding in Multiple Myeloma, *Am J Roentgenol* **30** 56, 1933

133 Wintrobe, M. M., and Buell, M. V. Hyperproteinemia Associated with Multiple Myeloma, *Bull Johns Hopkins Hosp* **52** 156, 1933

134 Denker, P. G., and Brock, S. The Generalized and Vertebral Forms of Myeloma. Their Cerebral and Spinal Complications, *Brain* **57** 291, 1934

135 Ehrstrom, M. C. Eine Studie uber die Bedeutung von Totalserumkalziumanalysen in der Klinik, *Acta med Scandinav*, supp 58, 1934, p 1

136 dalla Volta, A. L'iperglobulinemia quale varieta biologica dell'alterato ricambio proteico del mieloma, *Arch di pat e clin med* **14** 182, 1934

137 Cantarow, A. Bence-Jones Proteinemia in Multiple Myeloma, *Am J M Sc* **189** 425, 1935

138 Berglund, H., Medes, G., Huber, G. C., Longcope, W. T. and Richards, A. N. The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935, p 534

139 Case Records of the Massachusetts General Hospital, *New England J Med* **212** 204 and 353, 1935

serum was determined when indicated, but as the values were all within normal limits, they are omitted here

No	Patient	Sex	Age, Yrs	Serum				Primary Neoplasm	Site	
				Cal cium, Mg per 100 Cc	Inor- ganic Phos- phorus, Mg per 100 Cc	Phos- phatase, Bodansky Units per 100 Cc	Non protein Nitro gen, Mg per 100 Cc		Metastases in Bones	
I Cases of Metastatic Neoplasm of the Bone										
Group 1 Osteolytic Metastases										
1	N D	F	54	10.4	5.0	11.9	36	Breast	Skull, spine, pelvis, femurs, ribs, tibia, fibula, scapula, tarsus, carpus	
2	A G	F	42	10.2	3.9			Breast	Skull, pelvis, scapulas, spine, ribs	
3	E J	F	35	12.3	3.1	14.8	48	Breast	Skull, spine, pelvis, ribs	
4	P G	F	56	11.3	3.8	7.7	35	Breast	Skull, femurs, sacrum, pelvis	
5	M N	F	63	9.9	4.3	3.4	35	Breast	Pelvis, femurs, "osteomalacia carcinomatosa"	
6	G S	F	36	10.6	3.8	13.8	31	Breast	Pelvis, femur, spine, ribs	
7	M D	F	48	13.9	4.9	5.8	41	Bronchus?	Skull, spine, femur, pelvis	
8	A V	F	82	9.3	2.7	5.7	24	Lung	Pelvis, spine, ribs, skull	
9	J G	M	61	10.4	3.6	5.1		Prostate?	Pelvis, spine, ribs	
10	E T	F	40	11.4	3.4	6.5	31	Breast	Spine, pelvis	
11	S H	F	62	13.4	1.9	2.7	34	Skin	Pelvis, femur	
12	T H	F	49	10.8	3.4	3.3	27	Breast	Pelvis, femur	
13	M M	F	50	10.2	3.3	5.0	29	Breast	Pelvis, femur	
14	B R	F	59	9.9	2.8	3.4	31	Ovary	Pelvis, femur	
15	J T	F	38	10.4	4.2	5.5	26	?	Spine, pelvis	
16	M L	F	41	9.5	2.7	3.8	35	?	Spine, pelvis	
17	J C	F		10.4	2.5	3.6	26	Breast	Spine, pelvis	
18	A M	F	29	10.0	3.6	1.4	39	Uterus	Scapula, pelvis	
19	A F	M	58	9.8	3.3	5.9	32	Bronchus	Ribs	
20	H Z	F	74	9.1	3.2	2.6	31	Stomach	Femur	
Group 2 Osteolytic and Osteoplastic Metastases										
21	B H	F	41	13.1	2.9	6.4	34	Breast	Skull, pelvis, spine, ribs, scapula, humeri	
22	F R	M	65	10.2	3.5	8.1	28	?	Pelvis, femurs, spine, scapulas, humeri, skull	
23	E D	F	52	10.6	3.9	10.3		Breast	Pelvis, spine, femur, skull, ribs	
24	M	M		9.6	3.0	29.2	35	Prostate	Pelvis, spine	
25	L F	M	68	10.0	3.1	2.9	47	Hyper-nephroma (?)	Spine, pelvis, skull	
26	L S	M	58	9.1	3.2	7.6	22	Prostate	Pelvis, femur, sacrum	
27	J M	M	54	10.3	3.1	6.4	25	?	Scapula, pelvis, spine	
28	O S	F	38	10.8	4.1	37.7	28	Breast	Spine, pelvis, femurs	
29	C C	F	65	9.5	3.2	13.2	36	Thyroid	Skull	
Group 3 Osteoplastic Metastases										
30	W G	M	74	8.0	1.8	113.5	32	Prostate	Spine, pelvis, ribs, skull, clavicles, femurs	
31	A B	F	55	10.6	3.7	120.4	30	?	Pelvis, spine, humeri, clavicles, scapulas, skull, femurs	
32	W M	M	66	10.6	3.1	20.2	38	Prostate	Spine, pelvis, femur	
33	W M	M	42	9.5	4.2	20.1	57	Bladder	Spine, ribs, pelvis	
34	S H	M	64	9.2	2.0	16.0	35	Prostate	Pelvis, spine, ribs, scapula, humerus	
35	D D	M	58	9.5	3.6	14.0	33	Prostate	Pelvis, spine, femurs	
36	P P	M	70	10.7	2.9	3.9	31	Prostate?	Pelvis, femur	
37	G B	M	66	9.9	3.9	3.7	25	?	Pelvis (Paget's disease?)	
38	H S	F	72	9.6	3.3	3.2	25	?	Pelvis, femur (Paget's disease?)	
39	E K	M	69	9.8	3.6	4.5	29	Kidney?	Pelvis	
II Cases of Primary Neoplasm of the Bone										
40	C P	F	31	10.0	4.1	4.3	35	Osteoblastic type of osteogenic sarcoma, lumbar vertebra		
41	M S	M	16	11.0	4.2	5.0	24	Osteoblastic type of osteogenic sarcoma, jaw		
42	J A	M	7	9.6	2.8	6.9	20	Osteoblastic type of osteogenic sarcoma, femur amputation, metastases to lungs		
43	H L	F	10	9.6	3.5	5.6	20	Osteolytic type of osteogenic sarcoma, tibia		
44	S G	F	42	10.9	4.2	3.4	37	Osteolytic type of osteogenic sarcoma, humerus		
45	F P	M	10	10.3	3.3	8.8	27	Ewing's (?) sarcoma, lumbar vertebra		



The cases of metastatic carcinoma are divided arbitrarily into 3 groups, those in each group being arranged as far as possible according to the extensiveness of the skeletal metastases. Group 1 includes cases in which the metastases appeared roentgenographically to be entirely destructive of bone<sup>140, 141</sup>. Group 2 includes the cases in which both destruction and proliferative reaction of bone were obvious by roentgenographic examination. Group 3 includes the cases in which the metastases appeared roentgenographically to be entirely osteoplastic. In cases 1, 3, 4, 9, 17, 24 and 27 the patients were extremely cachectic and in some instances, moribund. This may account for the low normal values for the calcium content of the serum,<sup>142</sup> and the low inorganic phosphorus content<sup>143</sup> noted for several patients. In cases 1, 3, 4, 5, 8, 9, 17, 19, 24, 26 and 27 the spread of the metastases was rapid. These three distinctions appear to be more significant with respect to variations in the constituents of the blood than the age of the patient, the duration of the disease, the localization of metastases, etc. The number of variables in this group of patients is so large, however, that no wholly satisfactory correlation with the type of metastases, the cachexia of the patient or the rate of involvement of the bone could be established.

It would appear that elevations of the calcium content of the serum occur occasionally in cases of metastatic carcinoma of the bone. Values higher than 11 mg per hundred cubic centimeters were noted in 6 cases in 4 instances exceeding 12 mg. When hypercalcemia occurred, it was observed only in the presence of osteolytic metastases, chiefly when these were advanced and rapidly progressive. On the other hand, in cases 1 and 2, in which the most widespread osteolytic metastases were observed, an increase in the calcium content of the serum was not found on repeated examination. With few exceptions, the inorganic phosphorus content of the serum varied within normal limits. Values as low as 1.8, 1.9 and 2 mg per hundred cubic centimeters were observed in cachectic patients.

Extreme variations in serum phosphatase activity were observed in this group. In 12 cases the values were within the normal range. In 26 cases increases to 120.4 Bodansky units were noted. At least two

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140 Histologic study, however, almost invariably reveals evidence of some proliferation of the bone in such cases<sup>141</sup>.

141 Willis, R. A. *The Spread of Tumours in the Human Body*, London, J & A Churchill, Ltd, 1934, p. 335.

142 Jackson, H., Jr., and Taylor, F. H. L. Calcium, Potassium and Inorganic Phosphate Content of the Serum in Cancer Patients, *Am J Cancer* **19** 379, 1933.

143 Youngburg, G. E., and Youngburg, M. V. Phosphorus Metabolism. Distribution of Phosphorus in Normal and Cancer Bloods, *J Lab & Clin Med* **16** 253, 1930.

factors appear to be significant with respect to the level of the phosphatase activity of the blood in cases of carcinoma with metastases to the bones

1 The serum phosphatase activity may be greatly increased in the presence of widespread, actively progressive osteoplastic metastases and may reach levels as high as any seen in cases of advanced stages of Paget's disease (cases 30 and 31)

An Irishman (case 30), aged 74, a patient of Dr S A Beisler, underwent removal of a carcinoma of the prostate in 1930, the diagnosis being verified by histologic examination. Roentgenograms at that time showed no evidence of metastases to the bones or of Paget's disease. Metastases in the bones were first observed in 1932, with progressive and extensive involvement of the skeleton until the time of the patient's death in August 1934. Permission for autopsy was not obtained. We do not believe that the high values for phosphatase can be attributed to complicating Paget disease, for which there was no evidence. Whether metastases to the liver, not obvious clinically, contributed to the high values of phosphatase is not known. The bilirubin content of the serum was normal.

2 The serum phosphatase activity may be increased in cases of carcinoma with metastases to the liver, with or without jaundice. That the phosphatase activity of the blood is increased in patients with jaundice is recognized<sup>144</sup>. Roberts and Bodansky and Jaffe pointed out that the increase in phosphatase activity does not always parallel the degree of hyperbilirubinemia. We have observed increased serum phosphatase activity in cases of carcinoma in which jaundice was not present, the liver was not grossly enlarged or irregular and the bilirubin content of the serum was not elevated. In 6 such instances the presence of metastases in the liver, suggested only by the increase in phosphatase activity, was confirmed by exploratory celiotomy. One cannot always be certain, therefore, that the increased serum phosphatase activity found in many cases of carcinoma with metastases to the bone is not due in part to metastases in the liver which cannot be demonstrated clinically or by various laboratory procedures. We might add that in 4 cases in our series in which no clinical or chemical evidence of involvement of the liver was obtained and in which the serum phosphatase activity was within normal limits, definite hepatic metastases were noted at operation or at autopsy.

The phosphatase activity of the serum may be definitely increased in cases of carcinoma with osteolytic metastases to the bones, the values in 2 of our cases exceeding 12 Bodansky units per hundred cubic centi-

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144 Roberts, W M. Blood Phosphatase and van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, *Brit M J* **1** 734, 1933. Bodansky, A, and Jaffe, H L. Phosphatase Studies. IV. Serum Phosphatase of Non-Osseous Origin. Significance of the Variations of Serum Phosphatase in Jaundice. *Proc Soc Exper Biol & Med* **31** 107, 1933.

meters In 16 of the 19 cases in this series, however, the values obtained were less than 8 Bodansky units

Extensive studies of variations in the calcium content of the serum (reviewed by Jackson and Taylor<sup>142</sup>) and in the amount of inorganic phosphorus<sup>143</sup> in cases of neoplastic disease have appeared in the literature These show either normal or moderately lowered values Comparatively few observations have been made on the amount of serum calcium and inorganic phosphorus or on phosphatase activity in cases of carcinoma with extensive metastases to the bone The available data have been summarized Most of the authors cited have not distinguished between predominantly osteolytic and predominantly osteoplastic metastases in the bone, so we are unable to say whether the apparent differences demonstrated in our analyses explain in part the variable results recorded in the following tabulation

Year	Author	Case	Sex	Age, Yrs	Blood			Primary Neoplasm	Comment	
					Cal cium, Mg per 100 Cc	Inor ganic Phos phorus, Mg per 100 Cc	Phos pha tase, Units per 100 Cc			
1925	Andersen <sup>145</sup>	H	F	48	16.7	21.8		Breast	Metastases to femurs	
1929	Kay <sup>26</sup>						>1.3	?	Advanced metastases to spine and pelvis,	
1930	Alwens <sup>146</sup>				"Up to 16.8%"			?	"In occasional cases with osteoclastic metastases"	
1930	Kay <sup>147</sup>		F	41			0.44	?	Metastases to spine	
			F	56			0.74	?	Metastases to spine and pelvis	
			F	50			0.25	?	Metastases to pelvis	
			M	16			0.24	Femur	Periosteal sarcoma	
			F	17			0.63	Femur	Sarcoma	
1931	Brull et al <sup>148</sup>	F	F	52	11.6	12.9	5.6	Breast	Extensive metastases to bone	
1931	Jores <sup>111</sup>								"Occasional hypercalcemia in osteoclastic metastases"	
1931	Mason and Warren <sup>30</sup>		F	47	12.9	17.6	2.5	4.5	Breast	Extensive metastases to bone
1932	Aub and Farquharson <sup>115</sup>	M	F	47	10.7	10.5	5.1	3.9	Breast	Extensive metastases to bone
		N	F	53	9.3		3.6		Breast	Extensive metastases to bone
1932	Martin and Sarasin <sup>74</sup>		M		10.6	11.6	3.9		Prostate	Metastases to bone

145 Andersen, W. T. Some Researches on Calcium Content of Serum, Hospitalstid 68 1177, 1925

146 Alwens, W. Knochenerkrankungen in ihren Beziehungen zum Kalkstoffwechsel, zur inneren Sekretion und zu den Vitaminen. Klinik und Therapie vom Standpunkt des Internisten, Verhandl. d. Gesellsch. f. Verdauungs- u. Stoffwechselkr. 10 170, 1930

147 Kay, H. D. Plasma Phosphatase. II. The Enzyme in Disease, Particularly in Bone Disease, J. Biol. Chem. 89 249, 1930

148 Brull, L., Poverman, R., and Garin, M. Contributions à l'étude du métabolisme calcique. Osteoporose generalisée dans un cas de carcinomatose métastatique avec fractures spontanées multiples, Rev. belge sc. méd. 3 977, 1931

Year	Author	Case	Sex	Age, Yrs	Blood			Primary Neoplasm	Comment
					Cal cium, Mg per 100 Cc	Inor- ganic Phos- phorus, Mg per 100 Cc	Phos- pha- tase, Units per 100 Cc		
1932	Race <sup>149</sup>						1 56 1 30 0 45 0 18	? ? ? ?	Four cases of second- ary carcinomatosis of bone
1932	Solcard et al <sup>150</sup>	P	F	44	27 2 (whole blood)			Breast	Metastases to bone
1933	Brunschwig <sup>151</sup>	P	F	44	10 5	4 2		Breast	Metastases to bone
1933	Bulger and Gausmann <sup>154</sup>	22,810			14 9 15 1	2 5 2 7		Hyper- nephroma	Metastases to bone
1933	Centeno and Masciocchi <sup>152</sup>	L	F	40	12 0			Breast	Extensive metastases to bone
1933	Hoffmeister <sup>153</sup>				"Normal"			Prostate	Osteoclastic metas- tases, 4 cases
1933	Jackson and Taylor <sup>142</sup>		M	72	9 7			Prostate	Metastases to scap- ula and clavicle
				79	8 0			Buccal mucosa	Extension to bone
			M	60	7 6			Jaw	Invasion of bone
				72	7 2			Prostate	Extensive metastases to bone
				53	7 2			Skin	Involvement of bone
1933	Mocquot et al <sup>154</sup>	E	F	39	11 5-15 2			Breast	Extensive metastases to bone
1934	Bodansky and Jaffe <sup>32c</sup>		M	42	10 5	6 0	28 1	?	Metastases to bone
			F	38		5 5	9 4	?	Metastases to spine, pelvis and rib
			F	37	9 8	4 9	56-85	Bronchus	Extensive sclerosing metastases to skeleton
1934	Ehrström <sup>135</sup>	T	M	67	7 0 9 0			Prostate	Pelvis
1935	Robbins and Kydd <sup>96</sup>				18 5 11 6			?	Hypercalcemia in 5 cases with metas- tases to bone

Data on 6 cases of primary sarcoma of the bone are included in the summary on p 403. The serum phosphatase activity was essentially normal for persons of the ages of the respective patients in this series. Kay<sup>26</sup> found the plasma phosphatase activity to be 0.63 Kay units in a case of sarcoma of the femur. Jenner and Kay<sup>27</sup> reported a value of 11.5 Jenner and Kay units in a case of osteogenic sarcoma. Bodansky and Jaffe<sup>32c</sup> made examinations in 5 cases of osteogenic sarcoma. The

149 Race, J. The Phosphatase Test in the Arthritides and Osteitides, *Arch M Hydrol* **10** 6, 1932

150 Solcard, Rolland, and Quérangel des Essarts, J. Carcinomatose osseuse généralisée consécutive à un cancer du sein, *Ann d'anat Path* **9** 552, 1932

151 Brunschwig, A. Conversion of Osteolytic Carcinoma Metastases to Bone into Osteoblastic Ones by Large Doses of Calcium, *Proc Soc Exper Biol & Med* **30** 1293, 1933

152 Centeno, A. M., and Masciocchi, A. Cancer del seno y metástasis óseas, *Rev Asoc méd argent* **47** 2545, 1933

153 Hoffmeister, W. Blutkalkspiegel bei Knochenbrüchen und-erkrankungen, *Deutsche Ztschr f Chir* **240** 414, 1933

154 Mocquot, P., Herrenschildt, A., and Worms, R. Métastases diffuses du squelette chez des malades atteintes de cancer du sein, *Bull Assoc franç p l'étude du cancer* **22** 526, 1933

serum phosphatase activity varied from 3 to 166 Bodansky units. In 2 cases of Ewing's tumor the values were within the range observed for normal children. Franseen and Aub<sup>155</sup> reported increased values for plasma phosphatase in cases of osteogenic sarcoma. They expressed the belief that the determination of blood phosphatase may be useful in the early diagnosis of osteogenic sarcoma and in the detection of metastases.

#### COMMENT

The data summarized in the preceding pages permit certain inferences regarding the value and limitations of the determination of serum calcium, inorganic phosphorus and phosphatase activity in the differential diagnosis of the diseases of bone under consideration.

1 *Hyperparathyroidism*—When hypercalcemia, hypophosphatemia and increased blood phosphatase activity coexist, as in cases of uncomplicated classic hyperparathyroidism, confusion is unlikely. We have encountered similar findings only in an occasional case of carcinoma with advanced skeletal metastases in which the hypercalcemia was related, presumably, to neoplastic destruction of the bone, the hypophosphatemia, probably, to cachexia, and the increased blood phosphatase to involvement of the bone or liver. Difficulties in interpretation are due more frequently, in about one fifth of the cases of hyperparathyroidism, to the absence of consistent elevation of the calcium content of the serum above 12 mg per hundred cubic centimeters, they were due to the lack of consistent hypophosphatemia in approximately one half of the cases reported. Hypercalcemia is observed in many cases of multiple myeloma, in occasional cases in which extensive osteolytic carcinomatous metastases are present and, rarely, in other conditions<sup>156</sup> (case of E. M.). Hypophosphatemia occurs also in cases of osteomalacia and rickets. Increased blood phosphatase activity within the range observed in hyperparathyroidism may be encountered in cases of Paget's disease, rickets, osteomalacia, carcinoma with metastases to the bone and obstructive jaundice. It is apparent, therefore, as several observers have pointed out,<sup>157</sup> that while studies of the blood may be of great value in confirming or excluding the diagnosis of hyperparathyroidism, interpre-

155 Franseen, C. C., and Aub, J. C. Phosphatase Content of the Blood Plasma and Tumor Tissue in Malignant Diseases of Bone, *J. Clin. Investigation* **13** 698, 1934.

156 Rogoff, J. M., and Stewart, G. N. Further Blood Studies (Cholesterol and Calcium) in Control Adrenalectomized Dogs, *Am. J. Physiol.* **86** 25, 1928. Benedict, E. M., and Turner, K. B. The Serum Calcium in Polycythemia Vera, *J. Clin. Investigation* **9** 263, 1930.

157 Gutman, Swenson and Parsons.<sup>8</sup> Albright, Aub and Bauer.<sup>10a</sup> Robbins and Kydd.<sup>96</sup> Jores.<sup>111</sup>

tation of their significance without careful consideration of the clinical and roentgenologic aspects of the case may lead to grave error

*2 Paget's Disease*—It is an extraordinary fact that, in spite of the extensive skeletal changes which may take place in this disease, the content of calcium and inorganic phosphorus of the serum remains within normal limits. In this respect, as in many other clinical, pathologic and metabolic features,<sup>158</sup> hyperparathyroidism and Paget's disease differ so widely that it seems improbable that they could be different phases of the same disease, as some authors maintain. The finding of hypercalcemia in a case ostensibly one of Paget's disease should lead to a review of the evidence, since the literature contains several proved cases of hyperparathyroidism presenting roentgenologic features ascribed to Paget's disease.<sup>10</sup> As the only recognized abnormality of the blood in Paget's disease, the increase in phosphatase activity, first noted by Kay,<sup>26</sup> is of special interest. An unequivocal increase in blood phosphatase activity is demonstrable in almost all cases of polyostotic Paget's disease, in advanced stages of the disease reaching levels forty or more times the mean normal value. Successive determinations indicate that the level of serum phosphatase activity in most cases of Paget's disease remains remarkably constant for years.<sup>159</sup>

The degree of elevation of blood phosphatase activity varies widely for different patients with osteitis deformans. Kay<sup>147</sup> and others<sup>160</sup> have suggested that a rough proportionality exists between the extensiveness of the involvement of bone and the level of phosphatase activity, an observation corroborated by the distribution of values for serum phosphatase in the several groups of cases in our series (summary of cases of Paget's disease, p. 389). There are discrepancies in this relation, however (group 2 in the summary just mentioned), which have led to the suspicion that the activity of the osseous lesions may be another factor affecting the level for blood phosphatase in Paget's disease.<sup>160</sup> In some of our patients with unexpectedly high (or low) levels for serum phosphatase as compared with the extent of involvement of the bones revealed by roentgenograms, subsequent roentgenographic and clinical studies did, in fact, suggest unusually rapid (or slow) development of the disease.<sup>5c</sup> The determination of serum phosphatase may, therefore, prove to be of value in prognosis. We were unable to note any convincing correlation between the stage of the lesions in cases of Paget's disease or the localization of the process and

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158 Bauer, W. Hyperparathyroidism—A Distinct Disease Entity, *J. Bone & Joint Surg.* **15** 135, 1933.

159 Gutman, A. B., and Gutman, E. B. Paget's Disease—Relative Constancy of Serum Phosphatase Levels over Periods up to Two Years, *Proc. Soc. Exper. Biol. & Med.* **33** 150, 1935.

160 Bodansky and Jaffe<sup>32c</sup> O'Reilly and Race<sup>5b</sup>

the level for serum phosphatase. It was noted, however, as indicated in the summary of cases, that extensive involvement of the skull was almost invariably associated with relatively high values.

Since even widespread involvement by Paget's disease may be present without eliciting clinical symptoms or signs, the determination of serum phosphatase provides a useful means of corroborating the diagnosis as made by appropriate roentgenographic examination. However, the determination, in our experience, has been of little value in the diagnosis of early, localized Paget's disease, as the increase in serum phosphatase activity in such cases is likely to be unimpressive, and may be absent. In cases of more advanced disease the roentgenographic diagnosis is usually obvious, except in respect to differentiation from osteoplastic metastases in the bones. But in the latter condition, as has already been indicated, particularly in cases of carcinoma of the prostate, the serum phosphatase activity may also be markedly increased. Other diseases in which high levels for blood phosphatase are encountered have already been enumerated. The data at hand are in accord with Kay's conclusion<sup>32a</sup> that the increased blood phosphatase activity in cases of osteitis deformans is not specific and is probably a result rather than the cause of the disease.

3 *Multiple Myeloma*—The presence of hyperproteinemia<sup>102</sup> and hypercalcemia<sup>98</sup> or of either alone may provide valuable support for the diagnosis of multiple myeloma. These abnormalities are not demonstrable in many cases, however (table 3 and the summary of reports on multiple myeloma, p. 399), and when found they may disappear at irregular intervals or for long periods while the patient is under observation. In cases of diffuse involvement of the skeleton certain roentgenographic features of hyperparathyroidism may be simulated, and this fact and the frequent occurrence of hypercalcemia together with the rare observation of an equivocal enlargement of the parathyroid glands have led some investigators to postulate an associated state of "secondary hyperparathyroidism," as already mentioned. The inorganic phosphorus content of the serum is within normal limits except when renal insufficiency causes retention of phosphates. The serum phosphatase activity in cases of multiple myeloma, in contradistinction to that in cases of classic hyperparathyroidism, is usually essentially normal or only slightly elevated. Rowntree, however, stated that he encountered increased values in several cases<sup>161</sup>. The finding of Bence-Jones bodies in the urine is of value in differentiating multiple myeloma and hyperparathyroidism, since, with the possible exception of a single instance, Bence-Jones proteinuria has not been observed in cases of hyperparathyroidism.

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161 Rowntree, L. G. Progress Relative to Diseases of the Ductless Glands, Pennsylvania M. J. 36: 646, 1933.

4 *Metastatic Carcinoma of the Bone*—The occasional occurrence of hypercalcemia in cases of extensive osteolytic metastases in the bones may lead to confusion with hyperparathyroidism or multiple myeloma. Similarly, the increased serum phosphatase activity observed particularly in association with diffuse osteoplastic metastases in the bones may be confused with that found in cases of Paget's disease.

With regard to the physiologic significance of increased blood phosphatase activity, the fundamental work of Robison and his associates<sup>162</sup> led him to suggest that it is the result of an increase in specific cellular activities leading to formation of bone<sup>163</sup>. The data assembled in this study, apart from those concerned with conditions in which the increase is apparently of nonosseous origin,<sup>164</sup> are compatible with this view. The high values for blood phosphatase in Paget's disease<sup>26</sup> and in association with diffuse osteoplastic metastases in the bones are explained satisfactorily by this mechanism. In rickets, although excessive formation of bone does not occur, there is marked proliferation of cartilage cells, a fertile source of phosphatase, as Robison and Soames<sup>165</sup> have shown. The increased blood phosphatase activity in hyperparathyroidism, in which dissolution of bone is the most striking feature, would appear at first sight to be inconsistent with the conception that blood phosphatase is related to formation of bone. Histologic studies,<sup>166</sup> however, reveal extensive repair of bone concomitant with destruction, and the increase in blood phosphatase activity may be the result of such formation of new bone. This would explain why the level for blood phosphatase remains elevated so long and why it may even rise temporarily (case 1) after ablation of the parathyroid tumor. Albright, Aub and Bauer<sup>10</sup> have observed a rough correlation between the level of phosphatase in the plasma and the number of osteoblasts in sections of bone taken for biopsy after operation. A fair degree of correlation between the rate of redeposition of bone observed roentgenographically and the level for serum phosphatase was noted after operation in case 1 of our series. Whether the moderate increase in serum phosphatase activity

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162 Robison, R. The Possible Significance of Hexosephosphoric Esters in Ossification, *Biochem J* **17** 286, 1923

163 Robison, R. The Significance of Phosphoric Esters in Metabolism, New York, New York University Press, 1932

164 Bodansky, A. Phosphatase Studies. VI Non-Osseous Origins of Serum Phosphatase. Its Increase After Ingestion of Carbohydrates, *J Biol Chem* **104** 473, 1934

165 Robison, R., and Soames, K. M. The Possible Significance of Hexosephosphoric Esters in Ossification. II The Phosphoric Esterase of Ossifying Cartilage, *Biochem J* **18** 740, 1924

166 Schmorl, G. Zur Technik der Knochenuntersuchung. Bemerkungen zur Diagnose der Ostitis deformans Paget, Ostitis fibrosa v. Recklinghausen und Osteoporose, *Beitr z path Anat u z allg Path* **87** 585 1931



found in many cases of carcinoma with predominantly osteolytic metastases in the bones is due in part to a proliferative reaction of the bone not apparent in roentgenograms is an interesting speculation. In multiple myeloma, in which, it is said, proliferative reaction of bone is virtually absent, the increase in serum phosphatase activity is slight or absent, despite extensive involvement of the bone.

#### SUMMARY

The calcium and inorganic phosphorus content of the serum and the serum phosphatase activity were determined in 4 cases of hyperparathyroidism, 76 cases of Paget's disease, 6 cases of multiple myeloma and 45 cases of neoplastic disease of the bones. The relevant data from the literature are summarized. The usefulness and limitations of these determinations in the differential diagnosis of the diseases of bone under consideration are discussed.

1 Of the cases of hyperparathyroidism in which determinations are recorded in the literature, about four fifths showed consistent hypercalcemia, with a calcium content of more than 12 mg per hundred cubic centimeters, and about one half, consistent hypophosphatemia, with an inorganic phosphorus content of less than 2.5 mg. Increase in blood phosphatase activity was found in every case of classic hyperparathyroidism with definite changes in the bones in which determinations were made (28 cases). Complicating factors affecting these values and their significance in differential diagnosis are discussed. The question of "secondary" hyperparathyroidism is considered.

2 The calcium and inorganic phosphorus contents of the serum are within normal limits in cases of uncomplicated Paget's disease. The serum phosphatase activity is almost invariably increased in cases of advanced disease reaching values forty or more times the mean normal value. The level for serum phosphatase is roughly proportional to the extent of involvement of the bones and is probably affected also by the activity of the osseous lesions. In this sense, the determination may be of value in prognosis. Increased blood phosphatase activity is not specific for Paget's disease. The increase in instances of early, localized Paget's disease is often equivocal, so that the determination is of little value in such cases. Nor is it usually of assistance in differentiating cases of osteoplastic metastases in the bone, in which serum phosphatase activity is also increased.

3 Definite hypercalcemia has been observed in a number of cases of multiple myeloma. The inorganic phosphorus content of the serum is normal or somewhat elevated. The serum phosphatase activity is usually normal or slightly elevated.

4 Hypercalcemia is present in occasional cases of carcinoma with extensive, predominantly osteolytic metastases to the bones. The amount of inorganic phosphorus in the serum is usually within normal limits, but it may be depressed in cases of advanced cachexia or increased when renal insufficiency is present. The serum phosphatase activity is usually moderately increased or essentially normal.

In cases of carcinoma with extensive, predominantly osteoplastic metastases, the serum phosphatase activity may be as high as that in advanced Paget's disease. The content of calcium and that of inorganic phosphorus in the serum are normal, except when renal insufficiency is present. In cases of carcinoma with metastases to the liver, with or without jaundice, variable increases in serum phosphatase activity are observed.

5 The physiologic significance of increased serum phosphatase activity in cases of disease of the bone is discussed.

# NEUROPATHY IN DIABETES

## LIPID CONSTITUENTS OF THE NERVES CORRELATED WITH THE CLINICAL DATA

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Contact with many persons with diabetes impresses one with the frequency of neuropathy in these patients. A study of this neuropathy from any approach is likely to be interesting and helpful in the present state of knowledge about it. The clinicians have noted evidence of degeneration, and the pathologists have partially confirmed their findings. We attempted to investigate this degeneration from the point of view of the fatty constituents of the nerves. The stains used by the pathologists indicated damage to the lipid sheath of the nerves but did not reveal the character of the change in detail.

In a previous paper<sup>1</sup> we reviewed the appropriate literature and gave a preliminary report of the results of the chemical analysis of twenty nerves of diabetic patients as compared with nerves from persons without diabetes. In the present paper are included analyses of thirty-two more nerves from diabetic patients and a comparison of the entire series of fifty-two nerves obtained from forty-seven diabetic patients with twenty-three nerves from persons without diabetes. Individual values for nerves are listed in tables 1 and 2. The average phospholipid, cholesterol and cerebroside content of nerves from diabetic patients is much less than that of normal nerves.

The diabetic patients were of the elderly, sclerotic type and suffered from diabetes of mild or moderate severity. Their condition was not primarily diabetic neuritis, although twenty of them complained of pain, paresthesia or muscular paresis. Abnormal pupillary reactions were noted in four cases. Hemiplegia had occurred in case 11106. A diagnosis of thrombosis of the femoral artery was made in cases 5423 and 10582. Syphilis was present in case 10171, but there was no serologic evidence of involvement of the nervous system. In case 3575 it was suspected that the patient had pernicious anemia, but it was not

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1 Jordan, W R, Randall, L O, and Bloor, W R. Neuropathy in Diabetes Mellitus, Arch Int Med 55:26 (Jan) 1935

TABLE 1—*Analyses of Normal Nerves*

Case No	Nerve	Phospholipid		Cholesterol		Cerebroside		Water, per Cent	Phospho-lipid, Choles terol, per Cent	Phospho-lipid, Cerebro side, per Cent	Choles terol, Cerebro side, per Cent
		Moist Weight, per Cent	Moist Weight, Fat Free, per Cent	Moist Weight, per Cent	Moist Weight, Fat Free, per Cent	Moist Weight, per Cent	Moist Weight, Fat Free, per Cent				
7632	R femoral	4.51	4.85	1.11	1.17	1.78	1.90		4.05	2.54	0.63
7632	L femoral	4.94	5.37	1.61	1.73	1.61	1.73		3.06	3.06	1.00
62858	L femoral	4.93	5.35	1.45	1.56	1.13	1.21		3.40	4.42	1.30
62858	R femoral	4.44	5.05	1.32	1.44	0.70	0.77		3.36	0.84	1.89
46506	R femoral	3.72	4.60	1.16	1.42	0.86	1.06		3.21	4.34	1.35
46506	L femoral	4.17	5.05	1.05	1.25	1.01	1.20		3.99	4.13	1.04
75201	L femoral	4.55	5.60	1.39	1.71	1.54	1.88		3.28	2.95	0.90
53033	R femoral	4.80	5.04	1.48	1.54	1.63	1.70		3.25	2.95	0.91
62758	R tibia	4.05	4.15	1.86	1.97	2.45	2.62		2.18	1.65	0.76
72926	L sciatic	4.58	5.15	1.62	1.82	1.02	1.16		2.82	4.48	1.59
62428	L femoral	4.22	4.60	1.35	1.45	1.10	1.18	70.0	3.12	3.84	1.23
62428	R femoral	4.45	4.90	1.48	1.61	1.41	1.54	66.7	3.00	3.16	1.02
64097	L femoral	4.16	4.48	1.85	1.44	2.30	2.45	70.5	3.08	1.81	0.59
64097	R femoral	4.81	5.07	1.41	1.49	2.40	2.52	73.5	3.41	2.00	0.59
63216	R femoral	3.76	3.93	1.06	1.11	1.76	1.84	72.3	3.55	2.14	0.60
63739	L femoral	5.24	5.74	1.89	2.08	1.81	1.99	62.4	2.77	2.80	1.05
64411	L femoral	5.90	6.60	1.86	2.08	2.08	2.32	62.0	3.17	2.84	0.90
A2257	R femoral	5.06	5.54	1.77	1.88	2.05	2.24	61.0	2.87	2.47	0.86
53300	L femoral	4.30	5.85	1.46	1.58	1.20	1.29	60.8	2.95	3.58	1.22
53894	R femoral	3.26	3.55	1.19	1.30	2.75	3.00	68.4	2.74	1.18	0.43
70496	L femoral	5.75	5.90	2.40	2.45	1.76	1.80	58.0	2.40	3.27	1.36
11806	Femoral	4.80	5.04	1.48	1.54	1.63	1.70		3.24	2.84	0.91
91 185	Pelvic	4.00	4.55	1.66	1.91	1.18	1.35		2.41	3.38	1.41
	Average	4.54	5.04	1.49	1.63	1.61	1.76	65.5	3.10	3.14	1.02

TABLE 2—Analyses of Nerves from Diabetic Patients

Case No	Nerve	Phospholipid		Cholesterol		Cerebroside		Int. Moist Weight, per Cent	Phospho lipid, Choles terol, per Cent	Phospho lipid, Choles terol, per Cent	Choles terol Cerebro side, per Cent
		Moist Weight, per Cent	Moist Weight, Fat Free, per Cent	Moist Weight, per Cent	Moist Weight, Fat Free, per Cent	Moist Weight, per Cent	Moist Weight, Fat Free, per Cent				
1605	R posterior tibial	1.27	1.34	0.53	1.13	1.20	5.45	2.40	1.12	0.47	
2029	R posterior tibial	0.89	1.00	0.35	0.32	0.36	10.37	2.54	2.78	1.10	
2863	L posterior tibial	1.48	1.58	0.62	1.31	1.39	6.68	2.39	1.13	0.47	
3375	R femoral	1.91	2.04	1.11	0.31	0.36	4.07	1.75	5.70	3.26	
3375	L femoral	1.59	1.65	0.54	0.63	0.67	3.20	2.95	2.52	1.17	
3962	L posterior tibial	0.92	1.09	0.35	0.41	0.52	15.30	2.63	2.09	0.80	
5423	R anterior tibial	0.90	1.30	0.33	0.48	0.78	31.20	2.72	1.67	0.61	
5335	R posterior tibial	0.47	0.50	0.23	0.61	0.68	5.55	1.63	0.74	0.44	
6088	L external peroneal	1.75	2.62	0.53	1.03	1.56	13.60	3.30	1.67	0.50	
6088	L posterior tibial	2.18	2.51	1.19	1.18	1.17	13.70	1.83	1.85	1.01	
6115	L femoral	3.57	4.01	1.33	0.81	0.94	11.00	2.69	4.25	1.53	
6162	R femoral	2.24	2.30	0.79	1.83	2.06	11.10	2.84	1.23	0.13	
6177	R posterior tibial	1.62	1.77	0.76	0.71	0.82	9.41	2.90	2.19	0.76	
7052	R posterior tibial	1.44	1.63	0.36	0.85	1.00	11.15	2.57	1.64	0.64	
7465	L posterior tibial	0.52	0.54	0.23	0.21	0.52	4.15	2.25	1.04	0.46	
7575	L posterior tibial	1.49	1.81	0.38	0.76	0.92	17.60	3.92	1.96	0.30	
9191	L femoral	3.71	5.12	1.03	0.82	1.19	30.03	3.41	1.32	1.32	
9459	L posterior tibial	1.30	1.35	0.49	0.83	0.85	2.60	2.70	1.57	0.53	
9827	L femoral	3.81	7.15	1.15	1.62	2.97	46.00	3.35	2.41	0.72	
9931	R posterior tibial	1.27	1.46	0.33	0.63	0.76	13.40	3.81	1.93	0.50	
10092	L sciatic (thigh)	1.27	1.38	0.54	1.07	1.16	8.05	2.33	1.36	0.61	
10097	R posterior tibial	1.16	1.33	0.48	0.77	0.87	11.80	2.42	1.51	0.50	
10171	L posterior tibial	1.27	1.38	0.55	0.60	0.95	11.15	2.31	1.30	0.56	
10205	L sciatic (thigh)	1.40	1.62	0.76	1.07	1.23	13.80	1.84	1.31	0.71	
10205	L peroneal	0.87	1.00	0.39	0.61	0.72	11.15	2.23	1.36	0.61	
10207	R posterior tibial	0.31	0.38	0.19	0.46	0.46	16.45	2.94	3.48	1.18	
10382	L posterior tibial	0.91	1.13	0.32	0.36	0.15	19.00	1.63	0.86	0.53	
10677	R posterior tibial	0.48	0.51	0.21	0.11	0.46	16.45	2.94	3.48	1.18	
10712	L sciatic	3.38	3.87	1.20	0.91	1.01	11.10	2.28	1.17	0.51	
10712	L sciatic	2.55	3.02	0.91	1.11	1.11	15.00	2.71	2.26	0.83	
10723	R posterior tibial	1.10	1.20	0.40	0.53	0.53	8.55	2.75	2.24	0.82	
10760	R posterior tibial	0.78	0.91	0.23	0.41	0.49	17.60	2.78	1.71	0.62	
10791	R posterior tibial	0.83	0.93	0.21	0.35	0.51	12.90	3.16	1.03	0.42	
10799	R posterior tibial	1.03	1.16	0.42	0.97	1.09	33.15	4.45	5.60	0.81	
10803	L posterior tibial	0.73	0.83	0.16	0.13	0.15	14.65	3.22	3.43	1.03	
10804	R femoral	3.91	4.58	1.22	1.13	1.31	56.37	2.96	2.54	0.85	
10964	R posterior tibial	1.60	3.61	0.51	0.67	1.40	10.70	2.50	1.60	0.63	
10974	L posterior tibial	1.22	1.50	0.48	0.76	0.79	8.18	2.80	2.80	1.02	
11095	R posterior tibial	1.20	1.31	0.46	0.28	0.32	12.97	3.35	1.71	0.48	
11079	L posterior tibial	0.76	0.85	0.70	0.50	0.56	10.70	2.53	1.52	0.60	
11080	R posterior tibial	1.48	1.62	0.33	0.52	0.54	8.18	2.80	2.80	1.02	
11082	R femoral	3.16	3.60	0.89	1.03	0.96	12.97	3.35	1.71	0.48	
11082	R sciatic	2.10	2.2	0.87	1.57	2.13	8.42	3.09	3.09	1.23	
11083	L posterior tibial	0.93	1.03	0.31	0.61	0.71	1.15	1.92	0.70	0.37	
11106	L posterior tibial	0.63	0.63	0.22	0.27	0.28	18.48	2.95	1.07	0.36	
11108	R posterior tibial	1.10	1.63	0.15	1.40	1.70	11.10	2.15	0.75	0.31	
11128	R posterior tibial	1.50	1.66	0.60	0.87	0.93	8.57	2.27	1.77	0.78	
11144	L posterior tibial	1.12	1.81	0.50	0.54	1.11	7.35	2.21	1.35	0.60	
11147	Pelvic	1.80	2.06	0.63	0.76	0.88	13.05	2.86	2.37	0.83	
Path No											
14671	L posterior tibial	1.33	1.39	0.48	0.80	0.84	4.55	2.77	1.54	0.60	
16127	R posterior tibial	0.61	0.67	0.21	1.75	1.05	9.60	2.54	0.85	0.60	
12065	R posterior tibial	0.37	0.66	0.26	0.91	1.10	11.80	2.50	0.61	0.27	
	Average	1.40	1.82	0.50	0.83	0.99	13.84	2.67	2.01	0.76	

proved. Alcoholism of a great degree did not occur in this series and only three patients admitted using alcohol at all. A determination of the cholesterol content of the blood was made on nine patients, and the cholesterol level was found to be elevated only in case 6115.

In tables 3 and 4 are compared the average values<sup>2</sup> according to the level of the nerve examined. The increased pathologic change in the more peripheral portion of the nerve is striking. Only one nerve from below the knee contained as much as 2 per cent phospholipid, and in only two patients did the nerves at the pelvic level contain as little as 2 per cent phospholipid. This difference may vitiate to some extent the

TABLE 3—*Comparison of Average Values with Respect to the Level of the Nerve Examined*

Level of Nerve	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Pelvic	12	2.82	0.98	1.04
Thigh	2	1.34	0.65	1.07
Lower part of leg	38	1.08	0.42	0.76

TABLE 4—*Comparison of Lipid Values at Different Levels in Case 10205*

Name of Nerve	Level	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Sciatic	Thigh	1.40	0.76	1.07
Peroneal	Lower part of leg	0.87	0.39	0.64

TABLE 5—*Comparison of the Average Values with Respect to Age<sup>3</sup>*

Age	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
6th decade	10	0.99	0.39	0.70
7th decade	11	1.09	0.42	0.65
8th decade	14	1.14	0.45	0.91

\* Only the nerves of the lower part of the legs were studied.

results of the comparison of the nerves from persons without diabetes with the nerves from persons with diabetes, since only one of the nerves in the former group was from below the knee. The lipid content of this nerve, however, was similar to that of the nerves at the pelvic level from the same group. Furthermore, as will be seen later, a comparison of the pelvic nerves from persons without diabetes with the pelvic nerves from persons with diabetes confirms the pathologic changes exhibited by a comparison of the data in tables 1 and 2. Nevertheless, in diabetic persons the level of the nerve makes such a tremendous differ-

2 Comparison in all the tables includes only nerves from diabetic persons unless otherwise stated.

ence in the lipid values as to upset comparisons of the effect of other factors unless one utilizes nerves of a similar level. Its difference accounts for certain apparent influences reported in the former paper that seem less important now that we have enough specimens of the same level to compare. In the following comparisons are various possible influencing factors. We have indicated when only nerves of a similar level were used.

The ages of the patients ranged from 52 to 79.8 years. Our data indicate that age alone does not influence the chemical pathologic changes in the nerves of diabetic persons.

TABLE 6—*Comparison of Average Values with Respect to Arteriosclerosis\**

Degree of Arteriosclerosis	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Mild to moderate	6	3.19	1.04	1.16
Advanced	6	2.45	0.93	0.92

\* Only the pelvic nerves were studied.

TABLE 7—*Comparison of Average Values with Respect to Arteriosclerosis\**

Degree of Arteriosclerosis	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Mild to Moderate	5	1.42	0.56	0.81
Advanced	33	1.03	0.40	0.75

\* Only the nerves of the lower part of the legs were studied.

TABLE 8—*Comparison of Average Values with Respect to Circulation in the Lower Part of the Legs\**

Condition of Circulation	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Fair	6	1.23	0.44	0.83
Poor	32	1.05	0.42	0.65

\* Only the nerves of the lower part of the legs were studied.

Contrarily, vascular disease,<sup>3</sup> which in persons without diabetes is evidence primarily of advancing age, appears to affect the nerves adversely. This is illustrated by a comparison of nerves from patients with different degrees of arteriosclerosis or of circulatory deficiency of the lower part of the legs. At any given level, other factors being equal, these lipid constituents of the nerve will decrease with increasing arteriosclerosis. In this series we had no diabetic patient with normal arteries and circulation. It should be well worth while to make such a

3 In case 11005 we listed the arteriosclerosis as 2+ in our previous paper. Although this was true of the patient's arteries in general, we changed it in this paper to 3+ because of advanced arteriosclerosis in the leg from which the nerve was obtained.

study of young diabetic patients and of persons without diabetes with and without vascular disease. Two of our patients without diabetes had considerable arteriosclerosis and no diminution in the lipid values. In table 9 are compared the pelvic nerves from these two patients with the pelvic nerves from our diabetic patients. These data, though meager, tend to discourage the belief that the neuropathy of diabetes is due solely to arteriosclerosis.

TABLE 9—*Comparison of Average Values for Pelvic Nerves of Persons with Diabetes with Those of Persons Without Diabetes Who Had Arteriosclerosis*

Subjects	No. of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Those without diabetes	2	4.40	1.57	1.73
Those with diabetes	12	2.82	0.98	1.04

TABLE 10—*Comparison of Average Values with Respect to the Severity of Diabetes\**

Severity of Diabetes	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Mild	24	1.09	0.41	0.78
Moderate	11	1.14	0.45	0.78

\* Only the nerves of the lower part of the legs were studied.

TABLE 11—*Comparison of Average Values with Respect to the Duration of Diabetes\**

Duration of Diabetes, Years	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
0-2	8	1.01	0.41	0.60
2-10	15	1.10	0.43	0.82
10+	13	1.13	0.43	0.72

\* Only the nerves of the lower part of the legs were studied.

TABLE 12—*Comparison of Average Values with Respect to Previous Control of Diabetes\**

Control of Diabetes	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Good or fair	22	1.18	0.44	0.81
Poor	15	0.96	0.41	0.66

\* Only the nerves of the lower part of the legs were studied.

The diabetic factor responsible for the neuropathy has been very elusive, as it has been in clinical studies. Severity and duration seem equally blameless, although in such a small series we hesitate to make such a definite statement. Previous control of the diabetes is apparently of some importance, but is determined with some difficulty. Rarely has the patient been under strict supervision for sufficient time for us to



know that his diabetes has been well controlled. For this reason often we are forced to accept the patient's statements as to the tests of his urine at home. The test of the urine is not an adequate index, since there may be hyperglycemia and hypercholesterolemia when the urine is free from sugar.

The achilles tendon reflex in persons with diabetes shows decreased activity more often than the patellar reflex. We have compared the femoral and sciatic nerves to see if the chemical change reflects this

TABLE 13—*Comparison of Average Values of Femoral vs Sciatic Nerves at Pelvic Level\**

Nerve	No of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Femoral	8	3.00	1.01	1.13
Sciatic	3	2.65	1.00	0.91

\* One nerve was not labeled whether it was a femoral or sciatic nerve

TABLE 14—*Comparison of Lipid Values in Femoral and Sciatic Nerves in Case 11082*

Level of Nerve	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Femoral	3.16	0.59	1.85
Sciatic	2.10	0.87	0.68

TABLE 15—*Comparison of Average Values with Respect to Clinical Neuropathy\**

Reflex	No of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Normal	2	1.24	0.41	0.47
Absent	16	1.17	0.46	0.69
Both knee jerks and both ankle jerks absent	3	0.81	0.31	0.51

\* Only the nerves of the lower part of the legs were used

TABLE 16—*Comparison of Average Values with Respect to Clinical Neuropathy\**

Reflex	No of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Normal	5	3.18	1.07	1.02
Sluggish	2	3.09	1.01	1.48
Absent	1	1.80	0.63	0.76

\* Only the pelvic nerves were used

disparity in function. Our values show some slight increase in pathologic change in sciatic nerves as compared with the findings in the femoral nerves, but the number of specimens is too few to lend much force to this statement.

Chemical pathologic changes, as shown in tables 15 and 16, are greater in persons with clinical evidence of marked neuropathy than in

those without clinical evidence, but the correlation, as evidenced by the values for cholesterol and cerebroside, is not close. It seems that the chemical change exceeds or precedes the clinical change to a considerable extent.

#### SUMMARY AND CONCLUSIONS

Analyses of various lipid constituents of fifty-two nerves from persons with diabetes and of twenty-three nerves from persons without diabetes were made.

The average phospholipid, cholesterol and cerebroside content of the nerves from diabetic patients was considerably lower than that of the nerves used for controls.

The nerves from the lower part of the legs of diabetic patients showed much greater damage than nerves from the pelvic level. This was not true in the one nerve from the lower part of the leg of a control subject as compared with the pelvic nerves from control subjects.

The greater the vascular disease in a diabetic patient the greater the damage to the nerves. In two patients without diabetes who had arteriosclerosis this pathologic change was not found, indicating that vascular disease is not the sole cause of neuropathy in diabetic patients.

Previous inadequate control of the diabetes seems to affect the nerves adversely to a slight extent. The severity and duration of the diabetes seemed not to affect the nerves, or else the effect was nullified by other factors.

The chemical pathologic changes in the nerves of diabetic patients seemed to exceed or to precede the clinical manifestations of neuropathy.

More complete studies of this chemical pathologic change to determine the effect of numerous factors are necessary before reliable statements can be made.

# Progress in Internal Medicine

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## DISEASES OF METABOLISM AND NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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AND

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ROCHESTER, MINN

### I DISEASES OF METABOLISM

By DR WILDER

#### DIABETES MELLITUS

In the past year has been added what promises to be another outstanding achievement in the treatment of diabetes. This is the preparation by Hagedorn,<sup>1</sup> in Copenhagen, Denmark, of a compound of a protamine from salmon sperm and insulin. By virtue of a slow liberation of insulin a prolongation of the insulin effect is obtained, whereby wide fluctuations of values for blood sugar are avoided and the danger of reaction is lessened. The first printed announcement of the neo-insulin was made by Dr Elliott P Joslin<sup>2</sup> in the new edition, the fifth, of "The Treatment of Diabetes Mellitus". The information came after the manuscript of the book was completed, and the announcement appears as an added paragraph at the end of chapter 1.

The fifth edition of "The Treatment of Diabetes Mellitus" is itself a contribution of primary importance in the study of metabolism. It is more than a revision. It departs from the earlier editions in plan and organization, and while it loses thereby some of the charm, the friendly, fireside, chatty style of its predecessors, it becomes a more useful volume for study and reference. The author and his collaborators, Root, White and Marble, are to be congratulated on the systematic arrangement of

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From the Division of Medicine, the Mayo Clinic

1 Hagedorn, H C. Paper read at the meeting of the Nordisk Congress for Internal Medicine, Copenhagen, Denmark, June 29, 1935. Hagedorn, H C, Jensen, B N, Krarup, N B, and Wodstrup, I. Protamine Insulinate, J A M A **106** 177 (Jan 18) 1936. Root, H F, White, P, Marble, A, and Stotz, E H. Clinical Experience with Protamine Insulinate, J A M A **106** 180 (Jan 18) 1936.

2 Joslin, E P, Root, H F, White, P, and Marble, A. Treatment of Diabetes Mellitus, ed 5, Philadelphia, Lea & Febiger, 1935.

the subject matter as well as for the brevity. The pages number only 620, in the fourth edition there were 2 less than 1,000. Here at last is a treatise on diabetes worthy to take the place of the classic and heretofore unequalled second edition of the monograph of Bernhard Naunyn. Naunyn's "Der Diabetes Melitus" appeared in a second edition in 1906. Naunyn insisted on the spelling *melitus*, although ruefully admitting that he had few followers in this departure. The text was greatly shortened, made possible, he wrote, *weil das, was damals noch zu beweisen war jetzt längst anerkannt ist*.

What a triumphal march has been accomplished under Joslin's guidance since that time, thirty years ago! In his "Erinnerungen Gedanken und Meinungen" Naunyn<sup>3</sup> told of a visit by Joslin to him in Strasbourg. "It was characteristically American. Joslin wrote to ask if he might come for a brief visit. He would hardly be able to stay more than fourteen days. He came directly from Boston, with a stop of twenty-four hours in Paris. He actually remained little longer than three weeks, but the large amount of clinical material available and his great eagerness made it possible for him, in this short time, to acquaint himself with my views and principles. Then he traveled away again directly to Boston, with a twenty-four hour stop in Paris." This was the "Naunyn period" to which Joslin so frequently refers. His patients then died of uncontrolled acidosis, which now, in the "Banting period," is preventable, but the mortality, one can be sure, was not so high as it would have been except for the influence of Naunyn. What Naunyn was at the time of the visit in Strasbourg, Joslin became—the pre-eminent authority, master and leader in the field he chose to make his own.

In a reply to an inquiry by me regarding what he considers to be the most important new data incorporated in the new book, Dr. Joslin has supplied the following comments:

Page 28, table 1. In the year 1934 with 1,396,903 total deaths were 28,000 deaths from (with) diabetes, a rate per 100,000 population of 22.1 per cent, a ratio of diabetic to total deaths of 2.0 per cent.

Page 30, table 2. Diabetes is now the tenth disease and has advanced to this place from the twenty-seventh place in 1900.

Diabetes is not an old-age disease as shown by table 9 and fig. 1. I am much interested in this fact and so, too, are the Metropolitan people [Metropolitan Life Insurance Company]. We both feel that new data should be acquired about the onset of diabetes. You know that the ordinary history by a house officer is quite unreliable. One really must have the histories taken by someone who is deeply interested in them and will recheck the original answers of patients and earnestly try to find out when the disease began.

Page 44, third line from the bottom. The proportion of diabetic deaths to the total deaths among Jews between the ages of fifty-five and sixty-four years was

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<sup>3</sup> Naunyn, Bernhard. *Erinnerungen Gedanken und Meinungen*, Munich, J. F. Bergmann, 1925.

11.5 per cent or, in other words, one Jew in nine Jews died with diabetes in New York City at those ages. Please note I said died *with* diabetes and not *of* diabetes. I think that phrase worth carrying into literature.

Page 48, Diabetes in twins. Umber thought so much of the importance of his three cases of twins that he wrote quite an article about it (*Deutsche med Wchnschr*, 1934, no 15). Doctor White reports our series of thirteen similar and sixteen dissimilar twins. The table on page 50 (table 15) is a rather good one.

Page 173, table 45. In this table the changes from the Naunyn era to the later Banting era, in coma, cardiorenal-vascular diseases and cancer, are of chief interest. Incidentally on page 438 you will find that of our 256 cases of cancer there were 33 instances of primary cancer of the pancreas, or 13 per cent in contrast to about 2.5 per cent and 3 per cent which are the figures generally quoted. You will note, page 438, Rothmann found cancer in 3 of 22 diabetic autopsies, but of course that was just luck. However, I think that one should stimulate people to look for cancer of the pancreas in diabetics.

Page 241, table 57. The first line shows the increased duration of diabetes in numbers at different age periods which are large enough to be of some significance.

Page 242. You will see that in the later Banting period as compared with the Naunyn period there are ten times as many diabetics living over twenty years.

Page 243. The average age at death in the Naunyn era and the late Banting era rises from 44.5 to 62.8 years.

Page 299. Exercise, I think, is increasingly helpful, the work of Richardson<sup>4</sup> supplements the earlier work. Long before you can remember, I know, how we all wondered why it was that some diabetic patients were helped by exercise and others not, and now, of course, the whole point appears to be that for exercise to be helpful and to lower the blood sugar, one must have insulin and if one does not manufacture his own insulin then one must inject it and then exercise.

Page 382, Friedrich's ataxia. There is an interesting article on the subject which probably merits a comment (Curins, Storrington and Schomberg *Ztschr f d ges Neurol u Psych* **153** 719, 1935). It appears that there are ten authors in the literature who have noted a combination of Friedrich's ataxia with diabetes, a coincidence which the above authors state is too great for chance. The articles come from first-rate clinics, one of them was Umber's clinic.

Page 384. You will note that purulent infection of the urinary tract has been present in 18 per cent of 196 diabetic autopsies performed at the New England Deaconess Hospital since 1919. This last week Professor Thannhauser, in a clinic which he gave at the Boston Dispensary, emphasized the role of the kidney in diabetic coma. He said he thought that generally one could find some evidence of kidney involvement two or three days before the coma, and that the kidney really had much to do with the coma. Evidently he lays great emphasis on the amount of ammonia which is manufactured by the kidney.

Page 481. Fractures, I think, are worth studying. I believe they are really quite common in diabetics, but whether more common than in the non-diabetic population of similar age, I do not know. I noticed in the small group of diabetics I saw in Detroit the other day that 10 per cent had had fractures since their diabetes began. This is a subject for statistical investigation.

Page 509, table 106. Eight hundred thirty-nine diabetic children of whom 769 developed after August 7, 1922, and 70 had been seen earlier than that date, show 89 per cent survivors. One per cent has been untraced.

4 This fact was noted in the review of last year (Wilder and Wilbur<sup>45</sup>).

Page 516, Dwarfism This condition today is probably inexcusable

Page 528 Diabetes in children surviving ten years was put in simply to stimulate other people to publish their cases so that we may know what complications are to be expected

Page 534 gives a summary of the four preceding pages about children who either have done well, really did not have diabetes originally or were atypical cases We cannot believe there are any cures, but stated the results in this conservative fashion

Page 543 under section e shows data about hyper- and hypoglycemia in infants of diabetic mothers

Page 572 calls attention to the frequency of pentosuria, and, of course, you saw the article on pentosuria in twins in the Journal of the American Medical Association (Enklewitz, M, and Lasker, M Pentosuria in Twins, J A M A **105** 958 [Sept 21] 1935)

Page 573 Levulosuria has not been talked about much in this country and the paper by Silver and Reiner cited on page 573 stimulated us to hunt for a case

These are high spots The volume is a mine of information

*Suggestions on Therapy*—A therapeutic lead under investigation in several laboratories and clinics is what appears to be an antidiabetic activity of extracts of the mucosa of the duodenum Ivy and Fisher<sup>5</sup> obtained evidence of this in 1923, as did Heller<sup>6</sup> in 1929 The injection of Heller's extracts in normal rabbits, prior to an injection of dextrose, prevented as marked hyperglycemia as otherwise would occur and caused the sugar content of the blood to return more rapidly to a normal or subnormal level Laughton and Macallum<sup>7</sup> confirmed these observations both in dogs and in rabbits but noted that the sugar content of the blood of depancreatized dogs was not affected In their opinion the duodenal extract acted as a stimulant to the islands of Langerhans Heller,<sup>8</sup> in a recent report, names his extract duodenin He has observed that when given by mouth it reduces the sugar content after fasting of both men and rabbits, that it is not destroyed by pepsin and acid and that by treating it with pepsin and hydrochloric acid it can be made free from secretin La Barre and his associates<sup>9</sup> recently also have obtained positive results They use the term incretin for their extract of duodenal mucosa They noted (1) that with two dogs connected by

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5 Ivy, A C, and Fisher, N F The Presence of an Insulin-Like Substance in Gastric and Duodenal Mucosa and Its Relation to Gastric Secretion, Am J Physiol **67** 445 (Feb 1) 1924

6 Heller, H Ueber den blutzuckerwirksamen Stoff in Sekretinextrakten Arch f exper Path u Pharmakol **145** 343, 1929

7 Laughton, N B, and Macallum, A B Preliminary Note on Detection of Insular Hormone in Duodenum, Canad M A J **23** 348 (Sept) 1930

8 Heller, Hans Ueber das insulotrope Hormon der Darmschleimhaut (Duodenin), Arch f exper Path u Pharmakol **177** 127, 1935

9 La Barre, J, and Ledrut, J Sur l'origine pancreatique et tissulaire de l'action hypoglycémiant de l'incrétine preparée par hydrolvse pepsique Arch internat de physiol **40** 209 (Dec) 1934

pancreatic jugular anastomosis, that is, with the pancreatic vein of dog 1 emptying into the jugular vein of dog 2, the sugar content of dog 2 (the recipient) fell when incretin was given by vein to dog 1 (the donor), (2) that totally depancreatized dogs into which incretin was injected showed a drop in the value for sugar from levels between 225 and 310 mg per hundred cubic centimeters to levels between 70 and 35 mg, and (3) that depancreatized dogs could be kept alive for periods of months by the oral administration of incretin, provided the doses were made three or four times as large as those necessary to produce hypoglycemia by injection. Therefore, the authors concluded that incretin both stimulates the islands of Langerhans and promotes carbohydrate metabolism in a more direct manner.

Finally, Duncan, Shumway, Williams and Fetter<sup>10</sup> announce results in patients. With the Macallum-Laughton extract they obtained no evidence of benefit in persons with marked hyperglycemia, but an effect became discernible when insulin was used to control the diabetes and then was omitted. Thirty patients received active extracts. In 12 the disease was called severe. In 18 it was mild. Of the 12 with severe diabetes, 8, including 4 children, showed "a definite improvement," while 4, 3 adults and 1 girl of 16, showed no benefit. Of the 18 with mild diabetes, 11 were helped and 7 were not. The protocols of these clinical observations leave one with the impression that the favorable results, in most instances, were in cases of short duration. Many investigators have fallen into this trap. They forget that it is characteristic of diabetes to show a remission during the first year or two under any kind of management and that the value of a new form of treatment must be proved with cases of long duration. This criticism is not meant to be discrediting. The results with the patients are encouraging, and the observations in the laboratories are full of promise. A serious difficulty has been encountered in the preparation of the extracts. Some have been active and others inactive.

Carrying another therapeutic suggestion for the treatment of diabetes are studies of the effect of mixtures of fractions or isolated fractions of the vitamin B complex. Funk<sup>11</sup> originally observed that the symptoms of vitamin deficiency in pigeons were in direct relation to the amount of carbohydrate eaten and later observed, with von Schonborn,<sup>12</sup>

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10 Duncan, G. G., Shumway, N. P., Williams, T. L., and Fetter, F. Clinical Application of Duodenal Extract (Macallum-Laughton) in Diabetes Mellitus, *Am J M Sc* **189** 403 (March) 1935.

11 Funk, Casimir. Studies on Beri-Beri. The Probable Role of Vitamines in the Process of Digestion and Utilization of Food, *J Physiol* **47** 25 (Dec 13) 1913.

12 Funk, Casimir, and von Schonborn, Erwin. The Influence of a Vitamine-Free Diet on the Carbohydrate Metabolism, *J Physiol* **48** 328 (July 14) 1914.

that pigeons with polyneuritis showed hyperglycemia and diminution or absence of hepatic glycogen. These and other data led Mills<sup>13</sup> to the opinion that the requirement for vitamin B in persons with diabetes might be higher than normal and to the treatment of diabetic patients with acid-alcoholic extracts of plants. His results were about what Allen<sup>14</sup> obtained with myrtillin, an extract of blueberry leaves. Other investigators have made similar observations. Melcer<sup>15</sup> describes some benefit in 6 diabetic patients treated with the vitamin, and since then Donard and H. Labbé<sup>16</sup> and Binet, Fabre and Bargeton<sup>17</sup> have written on the subject. M. Labbé, Nepveux and Gringoire<sup>18</sup> have used a product of vegetable origin, said to be four times as strong in vitamin B activity as dried brewer's yeast of good quality. When fed to normal rabbits in doses of 15 Gm, it caused an increase in the stores of glycogen and glutathione of 140 and 30.5 per cent, respectively. When it was given to diabetic patients, it had little effect in 2, a stabilizing action on the sugar content in 1 and a favorable effect on the tolerance for carbohydrate in 9. The average increase in tolerance was equivalent to 46 Gm of dextrose. The protocols of these observations are not at hand, and hence it is impossible to evaluate the results. They appear to have much the same significance as those made by Mills<sup>13</sup>.

Von Drigalski<sup>19</sup> recently reviewed the literature on this subject and reports 10 cases of diabetes in which the patients were treated with yeast. He concludes that yeast has no influence on the glycosuria, acidosis, concentration of sugar in the blood, requirement for insulin or body weight of patients who have diabetes. He expresses the opinion that in persons with diabetes conditions are entirely different from

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13 Mills, C. A. Treatment of Diabetes with an Acid-Alcohol Extract of Plants Rich in Vitamin B, *Am J M Sc* **175** 376 (March) 1928.

14 Allen, F. M. Blueberry Leaf Extract. Physiologic and Clinical Properties in Relation to Carbohydrate Metabolism, *J A M A* **89** 1577 (Nov 5) 1927.

15 Melcer, A. S. Treatment of Diabetes with Vitamin B, *Polska gaz lek* **11** 89 (Jan 31) 1932.

16 Donard, E., and Labbé, H. Sur l'existence, dans les touraillons d'orge germée, d'une substance ayant un pouvoir hypoglycémique et agissant d'une façon analogue à l'insuline, *Compt rend Acad d sc* **194** 1299 (April 18) 1932.

17 Binet, L., Fabre, R., and Bargeton, D. Pouvoir hypoglycémiant d'un extrait aqueux de levure de bière, *Compt rend Soc de biol* **113** 235, 1933.

18 Labbé, Marcel, Nepveux, Floride, and Gringoire, J. D. Le rôle des vitamines B dans le métabolisme hydrocarboné. Leur emploi dans le traitement du diabète, *Bull Acad de méd, Paris* **109** 689 (May) 1933, Influence des vitamines B sur la teneur en glycogène et en glutathion du foie des lapins, *J de méd de Paris* **53** 501 (June 8) 1933, *Compt rend Soc de biol* **133** 152 (May) 1933. Gringoire, J. D. Les vitamines B. Leur rôle dans le métabolisme hydrocarboné. Leur emploi dans le traitement du diabète, Paris, E. Le François, 1933.

19 von Drigalski, W. B-Vitamine als Insulinersatz, *Arch f Verdauungskr* **57** 1 (Jan) 1935.



those which obtain in experimental animals, which show an influence of vitamin B on carbohydrate metabolism. In the meantime, however, Williams and his associates<sup>20</sup> have prepared pure crystalline vitamin B<sub>1</sub>, and in a preliminary report on the use of this, in doses of 10 mg a day, 5,000 international units, they state that favorable effects on tolerance were observed. The protocols are not given, and if the condition was in the early stages confirmatory observations must be obtained in cases of severe diabetes of long duration before much emphasis can be placed on the reputed results. Recent personal observations on the effect of crystalline vitamin B<sub>1</sub> in 6 "pedigreed" cases of long duration have not been very encouraging, but it seems not unlikely that some additional supply of vitamin B, particularly B<sub>1</sub>, may be distinctly beneficial, if not on the tolerance for carbohydrate at least on the general health of the patient. The large vegetable content of the diets of many diabetic patients is no guarantee that the supply of this indispensable food factor is adequate to provide for an organism which, like that of the polyneuritic pigeon, is handicapped in the matter of handling dextrose.

The attempt to affect the tolerance for carbohydrate by treatment directed at the pituitary gland was considered in the review last year. Merle<sup>21</sup> described the case of a woman 31 years of age with diabetes resistant to insulin. The glycosuria was more marked at the time of menstruation, an endocrine antagonist to insulin was suspected, and the pituitary was irradiated from both sides in eight treatments, two each week. The total dose corresponded approximately to one-third the sterilizing dose for the ovary. The output of sugar was less after this treatment than it had been possible to obtain before, even with large doses of insulin. Soskin, Mirsky, Zimmerman and Crohn<sup>22</sup> have attempted the clinical application of the observations of Barnes and his associates<sup>23</sup> on the inhibitory effect of estrogenic hormone on the anterior lobe of the pituitary. The results were the same as those with

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20 Vorhaus, M. G., Williams, R. R., and Waterman, R. E. Studies on Crystalline Vitamin B<sub>1</sub>. Experimental and Clinical Observations, *J. A. M. A.* **105** 1580 (Nov 16) 1935.

21 Merle, E. Diabète grave insulino-résistant. Réduction brusque et massive de l'insulino-résistance par irradiation de la région hypophysaire, *Bull. et mém. Soc. méd. d'hôp. de Paris* **51** 35 (Jan 21) 1935.

22 Soskin, Samuel, Mirsky, I. A., Zimmerman, L. M., and Crohn, N. The Role of the Anterior Pituitary Gland in Pancreatic Diabetes and Diabetes Mellitus, *Am. J. Physiol.* **113** 124 (Sept) 1935.

23 (a) Barnes, B. O., Regan, J. F., and Nelson, W. O. Improvement in Experimental Diabetes Following the Administration of Amniotone, *J. A. M. A.* **101** 926 (Sept 16) 1933. (b) Barnes, B. O., Culpepper, W. L., and Hutton, J. H. Experimental Diabetes Treated by X-Ray Applied to the Pituitary and Adrenal Regions, *Am. J. Physiol.* **113** 7 (Sept) 1935.

the dogs The well-being of the patients could be maintained when the administration of insulin was entirely omitted, and there was some "temporary alleviation of the hyperglycemia and glycosuria" Even in the presence of hyperglycemia and glycosuria no ketone bodies appeared in the urine This is less encouraging than might have been expected The work of Selle, Westra and Johnson<sup>24</sup> fails entirely to confirm the observations of Hutton,<sup>25</sup> mentioned last year, and those of Barnes and his associates reported more recently<sup>23b</sup> In five of seven diabetic depancreatized dogs the sugar content of blood drawn before breakfast was not reduced after irradiation of the pituitary, and no indication was found that the severity of the symptoms was diminished The authors call attention to the fact that the conditions of the experiments are different from those in subjects with spontaneous diabetes Their results, nevertheless, "sound a note of warning to workers contemplating the treatment of diabetes mellitus by irradiation of the hypophysis" They administered massive doses, such as one would not employ in treating a patient, doses three times enough to cause severe second degree burns if applied to the skin, and the degree of damage from such treatment to nerve structures and the other hormones of the hypophysis is conjectural They express the opinion that a better rationale must be had before treatment of diabetes by irradiation can be indorsed

*Effects of Salts of Sodium and Potassium in Carbohydrate Metabolism*—The existence of a reciprocal relationship between the metabolism of chlorides and that of dextrose has been suggested by various observations, such as the lower than normal levels, frequently, of chloride in the blood of persons with diabetes and the higher than normal levels, frequently chloride in the blood of persons with some states of hypoglycemia Also, when the chloride content of the blood is diminished, as occurs for instance with obstruction of the upper portion of the intestines or after the injection of histamine, the sugar content is said to rise In consequence, Glass and Beiless<sup>26</sup> were led to study the effect in persons with diabetes of the injection of hypertonic solutions of sodium chloride Schenk<sup>27</sup> had observed that the level of sugar fell after the injection of 100 cc of a 10 per cent solution of sodium chloride but had attributed it to dilution of the blood Glass and Beiless, into

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24 Selle, W A , Westra, J J , and Johnson, J B Attempts to Reduce Symptoms of Experimental Diabetes by Irradiation of Hypophysis, *Endocrinology* **19.97** (Jan-Feb) 1935

25 Hutton, J H , quoted by Wilder and Wilbur<sup>45</sup>

26 Glass, J , and Beiless, I Chlorhaushalt und Kohlenhydratstoffwechsel Einfluss hypertonischer Kochsalzlosung auf den Blutzucker bei Diabetes, *Ztschr f d ges exper Med* **73** 801, 1930

27 Schenk, quoted by Glass and Beiless<sup>26</sup>

10 diabetic patients, injected intravenously from 3 to 4 Gm of chemically pure sodium chloride in a 15 to 20 per cent solution and observed with great regularity that the values for sugar fell. The drop was from 12 to 43 per cent, averaging 25 per cent, of the original dextrose content of the blood. Hyperglycemia produced by the administration of dextrose was affected in a similar manner. Like results were obtained in 4 nondiabetic patients, although the effect in them was less striking. Sodium chloride by mouth in a dose of 12 Gm was equally efficacious. The results could not be explained by spontaneous fluctuations or by dilution of the blood. They were attributed to the chloride anion rather than to the sodium cation, because reported depressions of the sugar content of the blood following injections of sodium bicarbonate had never been of such significance. A vagotonic action on the part of the sodium chloride was suggested in explanation.

A much more elaborate study of the subject has been made by McQuarrie, Thompson and Anderson<sup>28</sup>. Two children with diabetes possessed an inordinate craving for table salt and required between 60 and 90 Gm daily to satisfy this craving. On account of this, 1 of the children, 3 other diabetic patients without the unusual craving, and 1 normal subject, all in the age group between 13 and 15 years, were subjected to the following investigation. They were given pure sodium chloride by mouth in doses of from 1 to 2 Gm per kilogram of body weight per day, with the result, in a period of from two to four days, that the body weight increased from 4 to 5 per cent, that the blood pressure rose to new plateaus between 30 and 50 per cent above former levels and, in the case of the diabetic patients, that the degree of glycosuria was markedly diminished and the sugar content of the blood before breakfast was brought down to considerably lower levels. The intake of food, dosage of insulin and activity remained unchanged. In the diabetic subjects the respiratory quotient before breakfast was slightly higher during the period of high intake of sodium chloride, ketonuria produced by the omission of insulin appeared later and the nitrogen balance, which previously had been negative, became positive, evidence of improved utilization of carbohydrate.

The sodium cation rather than the chloride anion was thought to be responsible for the phenomena observed by McQuarrie and his asso-

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28 McQuarrie, Irvine. The Effects of Excessive Salt Ingestion on Carbohydrate Metabolism and Arterial Pressure in Diabetic Children, *Proc Staff Meet, Mayo Clin* **10** 239 (April 10) 1935. McQuarrie, Irvine, Thompson, W H, and Anderson, J A. Effect of Excessive Ingestion of Sodium and Potassium Salts on Carbohydrate Metabolism and Blood Pressure in Diabetic Children, *J Nutrition*, to be published. Thompson, W H, and McQuarrie, Irvine. Effects of Various Salts on Carbohydrate Metabolism and Blood Pressure in Diabetic Children, *Proc Soc Exper Biol & Med* **31** 907 (May) 1934.

ciates, because sodium bicarbonate and sodium citrate, when given in amounts with equivalent sodium values, had similar even though less marked effects than those of sodium chloride. Also, the potassium cation was found to exert an opposite action. An ordinary diet high in potassium either prevented or greatly lessened the effects of sodium chloride, and potassium chloride in doses of from 10 to 20 Gm daily, together with a simplified diet low in sodium, resulted in a fall in blood pressure and a significant increase in the degree of glycosuria. When the two salts were administered together, one part of potassium was found to abolish completely the effects of at least three chemically equivalent parts of sodium. Attention is directed to the high values for potassium in the blood serum occasionally noted in untreated persons with diabetes mellitus. Only a few determinations of potassium have been made in the present study, but these indicate that high ingestion of sodium chloride is followed by a significant decrease of potassium in the serum, similar to that which occurs after the injection of insulin. This part of the study is as yet incomplete.

MacLean<sup>29</sup> likewise reported on the action on the carbohydrate metabolism of large doses of sodium chloride. A patient with relative insensibility to insulin, attributable to infected gangrene of a foot, received 40 Gm after each meal for three doses. That night a severe reaction to insulin occurred, and during the next fourteen days the requirement of insulin steadily declined from 115 to 55 units a day. Additional personal experience has led me to consider that saline therapy in persons with diabetes may be efficacious with doses of salt that are considerably smaller than those used by McQuarrie but that the usefulness of the procedure will be principally in the management of patients with relative insensitivity to insulin. In the well controlled case of a patient with severe but uncomplicated diabetes of ten years' duration, 15 Gm "extra" of ordinary table salt a day resulted in a fall of the requirement of insulin from a daily dose of 60 units to one of 40 units. The indication for reducing the dosage was the development of symptoms of reaction to insulin, but after about a week the requirement rose again to the original figure. On the other hand, in recent months I have seen repeatedly a favorable and lasting effect on patients who were insensitive to insulin because of infection or other complications. The subject is one which deserves much study, with particular attention paid to the balance of the sodium and potassium ions of the blood.

*The Diet for Patients with Diabetes*—The subject of what constitutes an optimal diet for the patient with diabetes continues to occupy the center of the stage, as it has since John Rollo first resorted to diet as a means

29 MacLean, A. R. Observations on Administration of Sodium Chloride in Diabetes, Proc Staff Meet, Mayo Clin 10 321 (May 22) 1935

of controlling the output of sugar in the urine. The pendulum swings now this way and now that, with reasonable arguments advanced for every departure. The subject was recently reviewed by Cardle,<sup>30</sup> and some of what follows is a part of the substance of his address. The two opposing extremes of dietary procedure were compared, the so-called high fat and the so-called high carbohydrate diets. In the procedure involving extreme limitation of carbohydrate, as first recommended by Peti n and almost simultaneously and independently by Newburgh and Marsh, emphasis was placed on the rigid restriction of protein. The calories were adequately supplied by fat, and it was found that nutrition could be maintained, acidosis avoided and hyperglycemia diminished. In a recent study Newburgh and Waller<sup>31</sup> showed that the tolerance of a diabetic patient, namely, the maximal capacity to dispose of the available dextrose from all sources without glycosuria in the absence of insulin, is not depressed by fat in the diet or augmented by carbohydrate in the diet and that the continued administration of the high fat content of maintenance diets does not lower it. In their opinion the efficiency of insulin in the human diabetic subject, as in the depancreatized dog, is related to the total amount of dextrose on which it acts. When the amount of available dextrose far exceeds the amount tolerated, each unit of insulin will cause the oxidation of 6 or 7 Gm of dextrose. Under otherwise similar conditions, except for a small excess of available dextrose, only 1 or 2 Gm is oxidized per unit of insulin. It has been the experience of Newburgh and Waller that 3 of every 4 diabetic patients can tolerate a diet high in fat and maintain themselves in a satisfactory state of nutrition without the use of insulin.

The divergent procedure, the diet high in carbohydrate and low in fat, has an ancient history. In 1500 B. C. an Egyptian prescription designed "to draw away the passing of too much urine" called for "a concoction of cakes, wheat grains, fresh grits, honey, sweet beer and berries." In the seventeenth century Willis advocated milk, rice and starch. The rice cure of von D ring came in 1868 and the potato diet of Moss  in 1898. Von Noorden's oatmeal cure and the combined cereal cure of Falta followed. The introduction of insulin brought with it the possibility of controlling glycosuria with diets of any type, and Geyelin, independently Sansum, soon afterward Poiges and Adlersberg and later Rabinowitch and others proceeded to take the fullest advantage of the new substitution therapy. These authors have all convinced

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30 Cardle, A. E. The Diabetic Diet, read before the Minnesota Society of Internal Medicine, Minneapolis, Nov. 11, 1935.

31 Newburgh, L. H., and Waller, Dorothy S. Studies of Diabetes Mellitus. Evidence that the Disability Is Concerned Solely with the Metabolism of Glucose, the Mode of Action of Insulin, *J. Clin. Investigation* **11** 995 (Sept.) 1932.

themselves of the desirability of their procedures, claiming that the well-being of the patient is improved, that a positive nitrogen balance is maintained more easily, that the danger of acidosis is diminished, that the tolerance for carbohydrate is improved and that the progress of arteriosclerosis is impeded. Mention was made in last year's review of Geyelin's report in the symposium of the New York Academy of Medicine. Since then he<sup>32</sup> has published a more extended account of his experience. Tuberculosis associated with diabetes was either cured or arrested in 21 of 26 patients. It has been impossible to secure follow-up records of all his 900 cases of diabetes in which treatment has been given during the past ten years, but in no patient who is at present under observation and in none of those who have been heard from has tuberculosis developed. Geyelin attributes this relatively low incidence of tuberculosis and also a relatively low incidence of gangrene and cardiovascular disease to the diet high in carbohydrate, but in the conclusion he adds the significant words, "normal calories." Geyelin's diets, in contrast to those in many clinics, are relatively high in caloric value, and this I think may contribute a great deal to his good results. Lukens<sup>33</sup> also believes that treatment has been improved by provision of a liberal allowance of carbohydrate, and Adlersberg,<sup>34</sup> who with Porges advocated a diet rich not only in carbohydrate but also in protein, again recounts the advantages to be obtained by this procedure. The addition of fat, he maintains, affects the metabolism unfavorably, even if the number of calories is not increased.

These reports are impressive, but like many clinical studies they do not provide conclusive evidence of the correctness of the views of their authors. If diabetic patients could be shut up in cages and fed strictly according to theoretical indications for a sufficient number of years, satisfactory answers might be obtained. As it is, I can claim with equal justification that the patients at the Mayo Clinic are doing just as well as those of Geyelin or Rabinowitch, if not better. My associates and I too have observed almost no tuberculosis and surprisingly little arteriosclerosis. There has been practically no arteriosclerosis in our young patients. The results of surgical procedure in our diabetic patients<sup>35</sup> certainly are as satisfactory as those to which Adlersberg refers, while

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32 Geyelin, H. R. The Treatment of Diabetes with Insulin (After Ten Years), Contrasting the Effects of Normal and of the Older Diabetic Diets, *J. A. M. A.* **104** 1203 (April 6) 1935.

33 Lukens, F. D. W. Carbohydrate in Diabetes. Newer Conceptions of Its Use, *Pennsylvania M. J.* **37** 992 (Sept.) 1934.

34 Adlersberg, D. Le régime pauvre en graisses dans le diabète simple (sans dénutrition), *Bull. gén. de therap.* **186** 58, 1935.

35 Walters, Waltman, Meyerdink, H. W., Judd, E. S., and Wilder, R. M. Surgery in Diabetes, *Minnesota Med.* **17** 517 (Sept.) 1934.

consistently for many years we have been prescribing diets that contain not over 110 Gm of carbohydrate, 70 Gm of protein and a good deal of fat. Like Geyelin, we have always insisted on adequate nutrition. The caloric requirement of the individual patient has been based on the assumption that the white collar worker and the housewife require food in an amount to exceed the basal caloric requirement for twenty-four hours by 50 per cent. Most of these calories come from fat, and therefore in many cases the amount of fat will equal or exceed 200 Gm. The diets are palatable, and the patients like them. They adhere to them with surprising faithfulness, and occasionally when we have tried to change to a diet high in carbohydrate in an individual case, the patient has objected.

*Cholesterol and Arteriosclerosis*—The high incidence of arteriosclerosis in diabetic persons, together with the frequent occurrence of elevated values for cholesterol and other lipoids in this disease, has induced some clinicians, particularly those who advocate diets high in carbohydrate, to conclude that the arteriosclerosis of diabetes is a result of feeding diets rich in fat. These clinicians have been influenced by the imbibition theory of Vichow as amplified by the Russians Amitschkow and Chalutow as well as by Aschoff. The subject of cholesterol and arteriosclerosis is exhaustively reviewed by Duff<sup>36</sup> of the department of pathology at the Johns Hopkins Hospital, with the following conclusions. The production of arteriosclerosis in rabbits by feeding cholesterol, as demonstrated by Amitschkow and Chalutow in 1913 and subsequently repeatedly confirmed by others, is not a valid reason for believing that an excess of cholesterol in the diet plays a part in the etiology of arteriosclerosis in man. The lesion produced in the rabbit is not identical anatomically with that of arteriosclerosis in man. The lesion in the rabbit involves the media primarily. The intima is first to be affected by the disease in man. The lesion in the rabbit is always dependent on hypercholesteremia, whereas hypercholesteremia is not observed with any regularity in human subjects with arteriosclerosis. The lesion in the rabbit is always associated with deposits of cholesterol in other organs and tissues, this has no counterpart in the arteriosclerosis of man. A uniform failure has accompanied all attempts to produce arterial lesions by feeding cholesterol to animals the diets and cholesterol levels of which are more comparable to those of man—cats, dogs, foxes and monkeys. This negative evidence is more important for application to human conditions than is the positive evidence from the experience with rabbits. Finally, those pathologic conditions in man which are associated with cholesterolemia, with the one exception diabetes, are infre-

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36 Duff, G. L. Experimental Cholesterol Arteriosclerosis and Its Relationship to Human Arteriosclerosis, *Arch Path* 20: 81 (July), 259 (Aug.) 1935.

quently associated with arteriosclerosis Duff refers to pregnancy, hypothyroidism, obstructive jaundice, certain types of nephritis and lipid nephrosis These negative observations in patients with outspoken hypercholesteremia constitute the strongest sort of evidence against the idea that hypercholesteremia acting alone can cause arteriosclerosis On theoretical grounds it might accelerate the development of arteriosclerotic changes previously initiated by some other agent, but there is little evidence at present that it plays even this small rôle

These also are the conclusions of Weiss and Minot<sup>37</sup> According to them, the evidence which has been brought forward in the attempt to demonstrate the relationship between the cholesterol content of the diet and the development of arteriosclerosis in man is equivocal and therefore not convincing Indeed, it would hardly influence an opinion not already prejudiced in favor of the idea The recent paper by Watson and Wharton<sup>38</sup> leads to the same conclusions These authors studied 112 dietary combinations as applied in 27 cases of diabetes and did not observe any significant disturbance of the cholesterol content of the blood, even with fairly extreme variations of the content of the diets in fat

Diabetes admittedly is a disease in which hyperlipemia and hypercholesteremia frequently are associated, but the metabolic disturbance of diabetes is by no means confined to the metabolism of lipoids Hyperglycemia, ketosis or the frequent occurrence of infections can just as well be held responsible for the arteriosclerosis in this disease Periodic dehydration, the frequency with which diets are inadequate in certain nutritional factors, such as some of the vitamins and salts, and the possibility that patients with diabetes require more than a normal supply of certain vitamins are other possible explanations Nor is it clear that the severity of the arteriosclerotic changes in persons with diabetes parallels the degree of elevation of the lipoids in the blood In a series of cases studied by Hunt<sup>39</sup> the most advanced arteriosclerotic changes appeared in the patients whose average cholesterol levels had been lowest Bearing on this general problem of arteriosclerosis is a recent report on the physical condition of Vilhjalmur Stephansson, the arctic explorer, who for eleven and a half years lived within the arctic circle and for a number of days totaling nine years was on an exclusive meat

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37 Weiss, Soma, and Minot, G R Nutrition in Relation to Arteriosclerosis, in Cowdry, E V Arteriosclerosis A Survey of the Problem, New York, The Macmillan Company, 1933, p 233

38 Watson, E M, and Wharton, Marion A A Comparison of Various Diets in the Treatment of Diabetes Mellitus, *Quart J Med* 4 277 (July) 1935

39 Hunt, Hazel M Cholesterol in Blood of Diabetics Treated at the New England Deaconess Hospital, *New England J Med* 201 659 (Oct 3) 1929



diet Lieb<sup>40</sup> reports extensive clinical and laboratory studies of Mr Stephansson and of another arctic explorer, who were placed on an "arctic" diet consisting exclusively of meat. The observations were made in the Russell Sage Foundation at Bellevue Hospital and continued for a full year in 1929. Stephansson's diet averaged about 2,650 calories, 2,100 of these consisted of fat and 550 of protein. The amount of carbohydrate in the meat varied between 30 and 50 calories a day. At this time the chemical composition of the blood was normal except for higher lipid values than ordinarily are regarded as normal. Since 1922, Dr Lieb has made an annual examination of Mr Stephansson, and the last of these is the subject of the present report. Mr Stephansson, although he is now 55 years of age, has remained in excellent general health and has gained in weight to 84 Kg as compared to 70.8 Kg in 1922. The examination revealed no significant abnormalities. The blood pressure was 120 mm systolic and 80 diastolic, the eye-grounds were normal, and the arteries, aside from "slight radial thickening," apparently were normal.

*Questionnaire on Diabetes*—In the *Medizinische Klinik* a number of outstanding clinicians, Falta<sup>41</sup> of Vienna, Schmidt of Prague, Umber of Berlin, Katsch of Griefswald and Porges of Vienna, supply brief answers to a number of stated questions, as follows: 1. Is the abnormality of the islands of Langerhans sufficient in every case of diabetes to account for the disease? 2. Are there various forms of diabetes? 3. May extra-insular diabetogenic factors alone provoke diabetes, or do they merely modify the clinical picture of the disease? 4. Is there an optimal diet for patients regularly receiving insulin? 5. Does muscle work modify the dextrose equivalence of insulin? 6. Does the symptom complex of spontaneous hypoglycemia depend on increased function of the island mechanism? 7. Are there any hormones besides insulin that are useful in the treatment of diabetes? The opinions on several of the topics vary as widely as would be expected. The answers nevertheless are interesting and instructive. On the subject of the diet, Porges' views are those of Adlersberg, previously mentioned. Katsch, Umber and Schmidt are of the opinion that the diet should be adjusted to the food habits and social status of the patient. Falta says that the optimal diet is that which best fits the individual patient. Since the requirement of insulin depends on the carbohydrate and protein content of the food, these must be held constant, but the amount of fat can vary within wide limits without great influence on the dose of insulin. There-

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40 Lieb, C. W. A Year's Exclusive Meat Diet and Seven Years Later, *Am J Digest Dis & Nutrition* **2** 473 (Oct) 1935.

41 Falta, W. Das endokrine System in der Pathologie und Therapie des Diabetes, *Med Klin* **31** 10 (Jan) 1935.

fore, one may leave the selection of the amount of fat to the appetite, the intake of calories being adjusted automatically. In some instances, however, mostly in those in which the equivalence of insulin in dextrose is low, a rich allowance of carbohydrate increases the equivalence, and the addition of fat depresses it. In such a case a diet high in carbohydrate may be used with advantage.

*The Theory of Diabetes*—The theory of diabetes upheld by Naunyn, Minkowski and Lusk, which regards failure in the metabolism of dextrose as the underlying disturbance in this disease, has been under attack from the beginning and continues so. Pfluger and von Noorden, Geelmuyden, Macleod and many others have crossed swords with its advocates. Now come Soskin,<sup>42</sup> a former pupil of Macleod, and his associates, with an extensive series of experimental observations supporting the alternate theory of glyconeogenesis.<sup>42d</sup> As I interpret the results, they show conclusively that the stability of the glycogen stores of the liver and possibly the rate of glycogenesis from protein are susceptible of modification by a variety of influences other than that exerted by insulin, they do not bear crucially on the all-important question of whether the large amount of sugar excreted by the diabetic organism is sugar made *de novo* from fatty acid. That is, they do not show that the liver can make more sugar than may be accounted for by glycogen, protein, lactic acid and glycerin. The experiments are ingenious, and it is extremely interesting that depancreatized dogs into which insulin and dextrose are injected continuously to maintain a constant blood sugar level react like normal dogs to the injection of extra sugar, the extra sugar causes a characteristic elevation of the blood sugar level, followed by a fall to below the "normal" level, exactly as occurs in the course of a dextrose tolerance test in a normal dog or man. This result upsets the idea that the dextrose tolerance test is a measure of the response of the pancreas and shows that the curves for the sugar content of the blood obtained in dextrose tolerance tests are imperfect indexes of the production of insulin.

In this connection research is reported by Ellis<sup>43</sup> of the Medical Unit, the London Hospital. Patients with severe diabetes were given

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42 (a) Soskin, S. Utilization of Carbohydrate by Totally Depancreatized Dogs Receiving No Insulin, *J. Nutrition* **3** 99 (Sept.) 1930. (b) Soskin, S., and Allweiss, M. D. Hypoglycemic Phase of Dextrose Tolerance Curve, *Am. J. Physiol.* **110** 4 (Nov.) 1934. (c) Soskin, S., and Mirsky, I. A. The Influence of Progressive Toxemic Liver Damage upon the Dextrose Tolerance Curve, *ibid.* **112** 649 (May) 1935. (d) Soskin, S., Allweiss, M. D., and Mirsky, I. A. Interpretation of Abnormal Dextrose Tolerance Curves Occurring in Toxemia in Terms of Liver Function, *Arch. Int. Med.* **56** 927 (Nov.) 1935.

43 Ellis, Arthur. Increased Carbohydrate Tolerance in Diabetics Following the Hourly Administration of Glucose and Insulin Over Long Periods, *Quart. J. Med.* **3** 137 (April) 1934.

dextrose at hourly intervals over periods of days, receiving no other food. Insulin was injected hourly. Although 600 Gm of dextrose a day was ingested in this manner, the dose of insulin required did not exceed that necessary with an ordinary restricted diet and in some cases was less. How is this to be explained? The observation is analogous to that referred to by Woodyatt<sup>44</sup> in the symposium of the New York Academy of Medicine mentioned in last year's review<sup>45</sup>. Ellis offers no explanation and nevertheless regards the observations as "difficult to reconcile with the generally accepted theory of pancreatic 'exhaustion'". Soskin's<sup>42a</sup> explanation would be that the "homeostatic regulation of the liver" was set at a higher level by the treatment with dextrose, so that the rate of endogenous production of sugar was diminished. Himsworth<sup>46</sup> would say that the amount of insulin kinase produced by the liver was increased, so that less insulin went farther. To my mind the subject is linked with that of sensitivity to insulin.

*Complications of the Eye in Diabetes*—Waite and Beetham<sup>47</sup> have compared observations on the eyes of 2,002 diabetic patients from the New England Deaconess Hospital with those on the eyes of 457 non-diabetic controls. The patients were selected consecutively as they were admitted to the hospital. The summary and conclusions are as follows: Patients with diabetes showed a high incidence of wrinkles in Descemet's membrane (patients with diabetes, 26 per cent, controls, 10 per cent), of deep retinal hemorrhage (patients with diabetes, 18 per cent, controls, 3 per cent) and of depigmentation of the epithelium of the iris (patients with diabetes, 6 per cent, controls, 2 per cent). On the other hand, the incidence of cataract of all varieties, except flocculi in patients with juvenile diabetes, was not greater in the diabetic persons. An equal incidence was noted also for uveitis, atrophy of the optic nerve and arcus.

Paresis of accommodation was demonstrated in 21 per cent of the diabetic patients, it was transitory, improving with treatment. An explanation may be that the deposition of glycogen in the pigment epithelium of the ciliary body hampers accommodation, on the other hand, frequent association with transitory changes in refraction suggests that alterations of the lens play a part. Abnormal deposits of glycogen

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44 Woodyatt, R. T., quoted by Wilder and Wilbur<sup>45</sup>

45 Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch Int Med* **55** 304 (Feb.) 1935

46 Himsworth, H. P. The Activation of Insulin, *Lancet* **2** 935 (Oct. 29) 1935

47 Waite, J. H., and Beetham, W. P. Visual Mechanism in Diabetes Mellitus. Comparative Study of Two Thousand and Two Diabetics, and Four Hundred and Fifty-Seven Non-Diabetics for Control, *New England J. Med.* **212** 367 (Feb. 28), 429 (March 7) 1935

were observed repeatedly in the retina, in the optic nerve, in the epithelium of the capsule of the lens and especially in the pigment epithelium of the iris and the ciliary body. The ciliary body in some cases was increased to many times its normal thickness by glycogen alone.

Transitory changes of refraction occurred in 6 per cent of the patients with diabetes. The errors of refraction were usually less than 2 diopters, the maximal change was 8 diopters. The changes did not occur in eyes from which the lens had been removed, aphakic eyes. The explanation is not wholly to be found in the sugar of the ocular fluids. The authors cite Granstrom as having demonstrated that the radius of the cornea is not altered and that no shortening or lengthening takes place in the axis of the globe. The disturbance is believed to be in the index of refraction of the lens, which is dependent on the retention of salt and the interplay of osmotic forces following precipitate shifts of the level of sugar in the blood.

TABLE 1—*Retinal Abnormalities (After Waite and Beetham<sup>47</sup>)*

	Visible Fundi in 3,915 Diabetic Persons Examined		Visible Fundi in 101 Nondiabetic Persons Examined	
	Number	Percentage	Number	Percentage
Deep retinal hemorrhages	730	18.6	34	3
Waxy exudates	420	10.7	7	0.7
Hemorrhage of nerve fiber layer	196	5.0	33	3
Cotton wool exudates	168	4.3	35	3
Iridescent crystals	28	0.7	4	
Proliferation of capillaries	26	0.7		

Senile and complicated cataracts occurred with no more frequency in the diabetic patients than in the nondiabetic persons, but cataracts were noted in 11 of 297 children. The characteristics in these juvenile cases, fine flocculi and iridescent crystals in the cortical levels, with later changes in the posterior cortex at the pole, were like those of the cataracts associated with parathyroid tetany, scleroderma and myotonic dystrophy.

The principal abnormalities of the retina and the incidence of these are shown in table 1.

Another recent study of diabetic retinitis is that of Wagener, Dry and Wilder.<sup>48</sup> The authors have compared observations in a series of 1,052 consecutive cases of diabetes, with the examination of the eyes made usually by one examiner (Wagener). Various types of hemorrhagic lesions of the fundus are described, with retinal photographs to illustrate

<sup>48</sup> Wagener, H. P., Dry, T. J., and Wilder, R. M. Retinitis in Diabetes, *New England J. Med.* **211** 1131 (Dec. 20) 1934.

them. The relative frequency of these types is indicated in table 2. It will be noted that the incidences of hemorrhagic lesions of all varieties are in fairly close agreement with those reported by Waite and Beetham.<sup>47</sup> The lesions occur predominantly in patients more than 40 years of age and usually, but not always, are associated with hypertension or other evidence of general vascular disease. Waite and Beetham observed that the lesions multiply with the continuation of diabetes but are not related to the age of the patient or to sclerosis of retinal vessels, vascular hypertension or renal disorders. They also demonstrate an absence of correlation with the dosage of insulin or the sugar content or calcium content of the blood. Wagener, Dry and Wilder comment on the frequency of the condition as compared with that observed in 1921 by Wagener and Wilder<sup>49</sup> (17.7 per cent in this study, 12.3 per cent in

TABLE 2—*Incidence of Retinitis in One Thousand and Fifty-Two Cases of Diabetes (After Wagener, Dry and Wilder<sup>48</sup>)*

Type	Male	Female	Total	Incidence, per Cent
A Typical of hypertension, not diabetic	4	8	12	1.1
B Diabetic				
1 Hemorrhages only	32	26	58	5.5
2 Hemorrhages with punctate exudates	32	35	67	6.3
3* Hemorrhages with punctate and cotton wool like exudates	15	16	31	2.9
4a Venous disease without proliferation	5	6	11	1.1
4b† Venous disease with proliferation	3	5	8	0.8
Total	91	96	187	17.7

\* This type represents the retinitis centralis punctata diabetica of Hirschberg.

† This type is the full blown retinitis proliferans.

the earlier study). This is accounted for by the longer lives at present of patients with diabetes. They lay particular stress on the finding of 23 patients (12 per cent of all diabetic patients who had hemorrhagic lesions of the retina) in whom retinitis developed in the absence of all clinical evidence of vascular disease. The lesion is usually mild in cases in which the condition is uncomplicated with other vascular disease, but its very existence must mean that the diabetes does something to injure the finer arterioles or venules of the retina.

In the series of Wagener, Dry and Wilder there were 66 patients whose eyes were examined two or more times over a period of several years, and from a study of the observations it appears likely that the retinal disease in question passes progressively through successive stages, beginning with hemorrhages only and eventuating in evident disease of the veins. The rate of progression is variable. Remissions

49 Wagener, H. P., and Wilder, R. M. The Retinitis of Diabetes Mellitus Preliminary Report, J. A. M. A. **76** 515 (Feb. 19) 1921.

occur occasionally, but the final stage is that marked by proliferative changes and hemorrhage into the vitreous, the so-called retinitis proliferans. It is suggested that the retinal vessels suffer injury in all cases of diabetes but that in four fifths of all cases the injury is insufficient to give rise to discernible hemorrhage or exudation. When the vessels are previously affected by other disease—nephritis, hypertension or atherosclerosis—it is more likely to do so. In that case a lesion characteristic of diabetes (punctate hemorrhages, deep exudates or visible disease of the larger retinal veins) is added to a retinal vascular lesion, otherwise characteristic of hypertension, arteriosclerosis or nephritis. The trained observer can diagnose diabetes correctly from the appearance of the retinal lesion whether this is simple or superimposed on a retinal abnormality produced by other conditions.

#### TREATMENT OF THINNESS WITH INSULIN<sup>1</sup>

The frequency with which hunger is precipitated when the sugar content of the blood falls during a reaction to insulin led to the thought that appetite might be stimulated with insulin in patients with anorexia and to the use of insulin for this purpose. In 1923 Pitfield<sup>50</sup> reported satisfactory results from treatment with insulin in 2 cases of infantile inanition, in 1924 Marriott<sup>51</sup> and Barbour<sup>52</sup> noted gains in weight in malnourished infants, and in 1925 Falta<sup>53</sup> reported on the use of the method in malnourished adults. In later papers Falta<sup>41</sup> expressed the view that the advantage was not entirely attributable to the improved appetite and suggested that insulin also favored the deposition of fat. The evidence for this opinion was sketchy. A flood of other papers has followed, and in the past year there have come to my attention one by Shepardson,<sup>54</sup> one by Nahum and Himwich<sup>55</sup> and one from Ann Arbor by a pupil of Newburgh, Freyberg<sup>56</sup>. In Shepardson's 17 cases the dosage varied from 20 to 64 units daily. The quantity was increased

50 Pitfield, R. L. Insulin in Infantile Inanition, *New York M. J.* **118** 217 (Aug. 15) 1923.

51 Marriott, W. McK. The Food Requirements of Malnourished Infants with a Note on the Use of Insulin, *J. A. M. A.* **83** 600 (Aug. 23) 1924.

52 Barbour, Orville. The Use of Insulin in Undernourished Non-Diabetic Children, *Arch. Pediat.* **41** 707 (Oct.) 1924.

53 Falta, W. Ueber Mastkuren mit Insulin und uber insulare Fettsucht, *Wien klin. Wchnschr.* **38** 757 (July 2) 1925.

54 Shepardson, H. C. Insulin Fattening in Ambulatory Patient. *California & West Med.* **40** 14 (Jan.) 1934.

55 Nahum, L. H., and Himwich, H. E. Insulin and Appetite. I. A Method for Increasing Weight in Thin Patients, *Am. J. M. Sc.* **183** 608 (May) 1932.

56 Freyberg, R. H. A Study of the Value of Insulin in Undernutrition, *Am. J. M. Sc.* **190** 28 (July) 1935.

to a point at which physiologic effects were manifest, but because of a variation in tolerance adequate doses were approached cautiously. The results were almost uniformly favorable. There were two types of increase in weight. In one group the gain was rapid and fairly continuous, in the other the gain was rapid at the beginning but became less marked with time and finally stopped, whether or not more insulin was given. A general improvement also was noticed, attributed to a tonic effect. Nahum comments on the feeling of pleasure in eating that appears. One of his patients, who was nauseated by the sight of food before treatment, developed a ravenous appetite and ate with satisfaction. He suggests that in persons with anorexia an actual inhibition of the secretion of insulin is mediated through the hypothalamus, accounting for the anorexia. Freyberg, on the other hand, expresses doubt, basing this on a careful study of 9 thin patients, who were treated without knowing that they were receiving insulin or that an increase in appetite or hunger was expected. The length of time that insulin was administered was from eight to forty-five days. The dose of insulin at the time the injections were stopped varied from 18 to 60 units, hypoglycemic reactions occurred on from one to three occasions in 4 patients. Only 2 patients had improved appetites, and only these 2 ate more during the course of treatment than before. They alone gained weight, and they had been gaining nearly as fast before. In another experiment, with 11 patients, Freyberg tested and compared the effect of a high caloric diet alone, the additional effect of a placebo and the additional effect of insulin. Good results were obtained in only 3 patients in the group receiving insulin, whereas with the placebo 4 patients had good, and 3 slight, benefit. This investigation suggests that the benefit from insulin in cases of thinness is not attributable to the insulin. However, psychic therapy is not undesirable in cases of anorexia nervosa, and experience shows that the prescription of insulin, with its attending threat of hypoglycemic reaction, is a very effective placebo.

#### DIABETES INSIPIDUS

The value of injection of solution of posterior pituitary in controlling the symptoms of diabetes insipidus was demonstrated independently in 1913 by Farini and Ceccaroni<sup>57</sup> and by von den Velden<sup>58</sup>. The results are satisfactory in most cases, but such treatment has the disadvantage of provoking extremely disagreeable side-effects, such as pallor, headache, palpitation and diarrhea. These disadvantages are avoided by spraying

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<sup>57</sup> Farini, A., and Ceccaroni, B. *Influenza degli estratti ipofisari sull' eliminazione dell' acido ippurico*, Gazz. d. osp. **34** 879, 1913.

<sup>58</sup> von den Velden, R. *Die Nierenwirkung von Hypophysenextrakten beim Menschen*, Berl. klin. Wchnschr. **50** 2083 (Nov.) 1913.

the substance into the nose or by applying it on cotton pledgets, as suggested by Blumgart,<sup>59</sup> unfortunately this is not always efficacious, and it is expensive. The administration of dry, powdered substance of the posterior lobe apparently is efficacious, more convenient and much less expensive. It was first suggested by André and Lucie Choay<sup>60</sup> in 1924 and later has been reported on favorably by Rosenberg,<sup>61</sup> Vidgoff,<sup>62</sup> Smith,<sup>63</sup> Canelo and Lissner,<sup>64</sup> Mainzer<sup>65</sup> and Adlersberg.<sup>66</sup> The economy is emphasized by Canelo and Lissner,<sup>64</sup> who treated a patient and noted that he required 1 cc of solution of posterior pituitary twice daily, whether administered hypodermically or in a spray, at a cost of from \$13 to \$15 a month, whereas a month's supply of material to be snuffed, consisting of one hundred and twenty measured  $\frac{1}{4}$  grain (0.016 Gm.) doses of posterior pituitary substance, cost only \$4 a month, a significant saving of about \$100 a year for "an equally efficient form of therapy." Each dose is weighed out and dispensed by the pharmacist in a "powder paper." When it is time for his medicine the patient unfolds the paper, rolls it up like a straw, inserts one end into the nostril and sniffs the powder. Four doses a day are required.

Mainzer describes 7 cases in which the nasal administration of powdered posterior pituitary substance controlled the thirst and polyuria of patients with normal neurologic and ophthalmic findings. He observed, as others have, that persons with diabetes insipidus secondary to encephalitis, basilar syphilitic meningitis and tumor are relatively insensitive to pituitary medication in any form. The feeling of thirst of Mainzer's patients disappeared in ten minutes. The diminution of

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59 Blumgart, H. L. The Antidiuretic Effect of Pituitary Extract Applied Intranasally in a Case of Diabetes Insipidus, *Arch. Int. Med.* **29**: 508 (April) 1922.

60 Choay, André, and Choay, Lucie. Traitement du diabète insipide par des inhalations d'extrait de lobe postérieur d'hypophyse, *Rev. neurol.* **1**: 267 (Feb.) 1924.

61 Rosenberg, Max. Zur Schnupfpulver-Therapie des Diabetes insipidus mit verschiedenen Hypophysen-Hinterlappen-Präparaten, *Klin. Wchnschr.* **9**: 152 (Jan. 25) 1930.

62 Vidgoff, Ben. Posterior Pituitary Therapy in Diabetes Insipidus, *Endocrinology* **16**: 289 (May-June) 1932.

63 Smith, F. M. Diabetes Insipidus. Treatment by Intranasal Insufflation of Posterior Lobe Pituitary Powder, *J. A. M. A.* **102**: 660 (March 3) 1934.

64 Canelo, C. K., and Lissner, H. A Case of Diabetes Insipidus Controlled with Powdered Pituitary Posterior Lobe Extract Applied Intranasally, as Snuff, *California & West Med.* **42**: 178 (March) 1935.

65 Mainzer, Fritz. Ueber Fragen der Hypophysenhinterlappentherapie des Diabetes insipidus, *Wien. Arch. f. inn. Med.* **26**: 101, 1934.

66 Adlersberg, D. Dauertherapie des Diabetes insipidus, *Ztschr. f. klin. Med.* **128**: 598 (Sept.) 1935.



diuresis lasted from eight to ten hours. As continued treatment led to compensation, there was considerable loss of weight, suspension of treatment being followed by a gain of weight up to 5 Kg. This observation is in conflict with the theory which regards the thirst of patients with diabetes insipidus as due to dehydration. In some cases an increased tolerance for water followed treatment, analogous to the increased tolerance for sugar in persons with diabetes mellitus after treatment with insulin, that is, after a time smaller amounts of the nasal powder sufficed to control the symptoms. The powder was diluted with lactose. There is no need for this, the undiluted powder is nonirritating.

Adlersberg<sup>66</sup> describes the cases of 2 patients treated effectively with powdered posterior pituitary substance for seven years, with no ill effects. The disturbance of water balance remained unaltered. Other medication is of little benefit in cases of diabetes insipidus. The estrogenic hormone appeared to be beneficial in a case reported by Troisier,<sup>67</sup> but it was without effect on 2 patients studied by Adlersberg. The administration of mercurial diuretics, aminopyrine and ergotamine, as well as the restriction of salt, is considered to be much less effective than treatment with solution of posterior pituitary or posterior pituitary powder, nevertheless it is of some usefulness in patients resistant to preparations of posterior pituitary.

A study of the composition of the blood and its variation under diverse influences, such as thirsting, restriction of salt and treatment with pituitary substance, is the subject of reports by Decourt and his associates<sup>68</sup>. The thirst in persons with diabetes insipidus, he concludes, is not related to the high values for chloride observed both in the plasma and in the corpuscles in the blood but is rather due to a diminished content of water, namely, a loss of the hydrophilia of the colloids of the tissues.

An interesting report based on the pathogenesis of diabetes insipidus is that of Biggart<sup>69</sup>. The theories of diabetes insipidus are reviewed. The current theory is based on the observations of Aschner<sup>70</sup> and of

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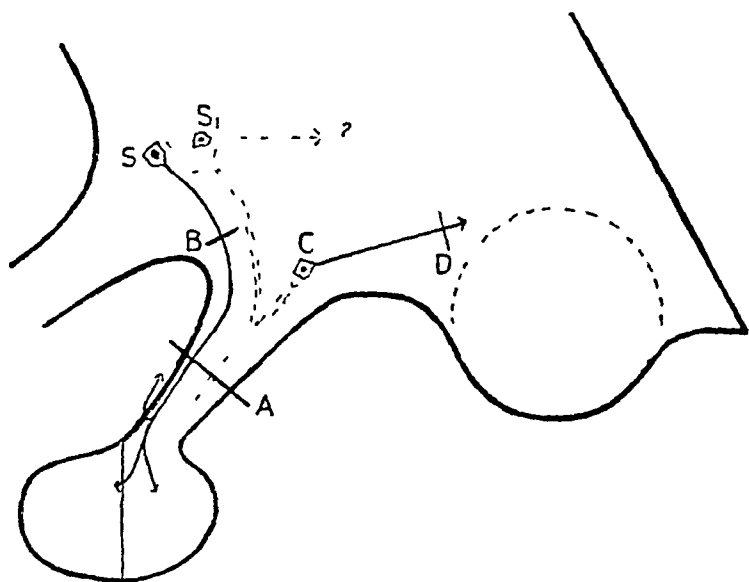
67 Troisier, Jean. Action antipolyurique des hautes doses de folliculine dans le diabète insipide de l'homme, *Bull et mem Soc med d hôp de Paris* **48** 1451 (Nov 18) 1932.

68 Decourt, J. Diabète insipide. Etude de la composition du sang et de ses variations sous diverses influences (régime dechlorure, traitement hypophysaire, épreuve de la soif), *Bull et mém Soc méd d hôp de Paris* **51** 468 (March 25) 1935. Decourt, J, Meyer, L, Audry, M, and Lesourd, R. Diabète insipide. Action du régime dechlorure sur la polyurie. Considerations sur l'élimination des chlorures, *ibid* **50** 1695 (Dec 24) 1934.

69 Biggart, J H. Diabetes Insipidus, *Brain* **58** 86 (March) 1935.

70 Quoted by Bailey and Bremer<sup>71</sup>.

Camus and Roussy,<sup>70</sup> who showed that hypophysectomy in itself did not produce polyuria but that examination of those animals in which the syndrome developed always revealed a lesion in the floor of the third ventricle. This view was confirmed by Leschke,<sup>70</sup> Houssay<sup>70</sup> and Bailey and Bremer,<sup>71</sup> who observed that injury of the infundibulotuberal region of the hypothalamus produced polyuria. It is also confirmed by Richter,<sup>72</sup> who has succeeded in producing permanent polyuria in cats by means of experimental lesions accurately placed in the region of the chiasm. The occurrence of diabetes insipidus in association with epidemic encephalitis, whether during the acute phase or as a sequel, has further emphasized the importance of the hypothalamus in the pathogenesis of the disease.



A diagram to illustrate the sites of the lesions producing diabetes insipidus. *S* indicates the nucleus supra-opticus, *S*<sub>1</sub>, the tract described by Greving, *C*, the position of the tuberal nuclei, *C-D*, the descending tuberal tract, and *A, B, C, D*, possible sites of injury (after Biggart<sup>69</sup>).

Biggart describes 3 cases of diabetes insipidus to illustrate how lesions affecting different regions of the hypothalamus produce the disease and to explain why extracts of the posterior lobe of the pituitary gland are active in controlling the disease in some cases and not in others (figure). He says:

A lesion at "A" may produce a polyuria by interruption of the supra-optic-hypophyseal tract. This division would presumably lead to a diminution of the

<sup>71</sup> Bailey, Percival, and Bremer, Frédéric. Experimental Diabetes Insipidus, *Arch Int Med* **28**:773 (Dec.) 1921.

<sup>72</sup> Richter, C. P. Experimental Diabetes Insipidus, *Brain* **53**:76 (April) 1930.

secretion of the antidiuretic factor, but this would be compensated for by the pars tuberalis which escapes. In fact according to Rubio the pars tuberalis will hypertrophy. A lesion at "B" will cut off the secretory fibers to the whole epithelial investment of the pars nervosa and pars tuberalis [of the pituitary], and so lead to the establishment of a permanent diabetes insipidus. Such a case, however, will be controllable by injections of pituitrin as the effector pathway from the nuclei of the tuber cinereum is still intact. A lesion at "C" or "D," however, which destroys the effector pathway, will result in a polyuria which is refractory to treatment. According to Dreyfus, such cases are rare in human pathology, and constitute but 5 per cent of all cases of diabetes insipidus.

Other writers place the percentage of these refractory cases at a higher figure. Cases of basal meningitis, syphilitic or otherwise, fall in the category.

A rôle in the pathogenesis of diabetes insipidus is attributed to the anterior lobe of the pituitary gland by Richter<sup>73</sup>. Total and partial hypophysectomy was performed on rats by a technic modified from that of Smith<sup>74</sup> and described in an earlier paper. The results were as follows. Total removal of the gland produced temporary diabetes insipidus in only twenty-eight of thirty-four animals and permanent diabetes in none. On the other hand, when the posterior lobe was removed entirely but a part of the anterior lobe was left, the diabetes in all the twenty-six animals proved permanent. These observations confirm the findings of von Hann<sup>71</sup> made in 1918 in a study of records made at autopsy on patients with diabetes insipidus. He noted that 20 patients suffering from this illness had lesions of the posterior lobe of the pituitary, with parts of the anterior lobe still intact, while 9 patients with much the same lesion but with the anterior lobe gone showed no diabetes insipidus. The experimental observations of Richter have been confirmed in Herbert Evans' laboratory by Pencharz, Hopper and Rynearson<sup>75</sup>. Their significance as yet is not entirely clear. The suggestion is made that the anterior lobe is responsible for a hormone with an action antagonistic to posterior pituitary.

## II NUTRITION

BY DR. WILBUR

Since the advent of the "vitamin era" greater interest has been shown by the people of civilized countries in the quality and kind of their food than in its quantity. Such a change in thought may prove to be one of the greatest public health movements of history if one can translate

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73 Richter, C. P. Experimental Diabetes Insipidus. Its Relation to the Anterior and Posterior Lobes of the Hypophysis, *Am. J. Physiol.* **110** 439 (Dec.) 1934.

74 Quoted by Richter.

75 Rynearson, E. H. Personal communication to the author.

the results of experiments on the nutrition of animals in terms of nutrition of man and if the present economic depression is not too prolonged McLester<sup>76</sup> well summarized this in his address entitled "Nutrition and the Future of Man," pointing to the tremendous influence of ridiculously small amounts of food and the influence man may have on his own destiny by taking them into consideration. During the period of twenty years from 1906 to the present, under conditions that were not varied except for improvement in ration, the normal standard rate of growth of the albino rat has tripled and the standard weight for the species has doubled. This improvement apparently has included all phases of physical development. Evidence also has been presented by McLester to demonstrate the improved physical condition and increased growth of Oriental and European immigrants to countries where life under improved nutritional conditions is possible. Studies in certain schools and universities in the United States and in England demonstrated an increase in the physical height of students over that of students of a generation ago. That increased physical efficiency may occur along with increased physical stature is indicated by studies in English schools and in the English flying corps. While the advantages of increased rate of growth are still debated, most physiologists apparently feel that the results are wholly favorable. While the potentialities of the human race for increases in longevity and improvement in vitality and vigor cannot be estimated, it must be admitted that they are great under circumstances of ideal conditions of nutrition.

The recent economic depression has affected the available supplies of food for the people of many countries throughout the world. Interest is focused again, as it was during the World War, on the problems of what constitutes undernutrition and adequate nutrition and how the latter may best be obtained for those who are in unfortunate economic circumstances. During the past year there have been interesting contributions to the problem of what constitutes malnutrition or undernutrition. Apparently, the old standard of body weight (of a child) compared with a table of standards in which the height may or may not be taken into consideration must be considered inadequate in terms of modern conceptions of nutrition. Even such studies as those made to differentiate the desirable weight ratios for children of various types of habitus through recognition that the size of the skeleton will determine the amount of soft tissues appropriate for an individual child, as noted by Boyd,<sup>77</sup> while an advance over older methods, must still be con-

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<sup>76</sup> McLester, J. S. Nutrition and the Future of Man, *J. A. M. A.* **104** 2144 (June 15) 1935.

<sup>77</sup> Boyd, J. D. Normal Nutrition During Childhood. Critical Review, *J. Pediat.* **6** 249 (Feb.) 1935.

sidered inadequate. In fact, it is questionable whether physical measurements will prove adequate criteria in the determination of the nutritional state of the individual subject. An interesting presentation of this subject was a discussion on the assessment of the state of nutrition<sup>78</sup> held before the Section of Epidemiology and State Medicine of the Royal Society of Medicine. It was pointed out that one of the main reasons for the present confusion is oversight of the fact that the state of nutrition is dynamic and not static. Account must be taken of the fact that the state of nutrition of the individual subject in large part is a resultant of physiologic processes and therefore that a wide range of adaptability to varying circumstances is possible. "Primary" malnutrition, which is the result of dietary deficiency, must be contrasted with "secondary" malnutrition, attributable to other causes, such as disease of the gastro-intestinal tract or other organs. There are at present no sufficient physiologic criteria of adequacy of nutrition in many of its aspects. Consequently, there is little wonder that so much variability exists in studies of the incidence of malnutrition. At present one must be content perhaps with such anatomic standards as the height and weight and with such physiologic measures as the turgor of the tissues, color of the skin and mucous membranes, degree of alertness, evidence of apathy or irritability, poor posture, restlessness, disturbed sleep and signs of fatigue,<sup>79</sup> as well as with clinical estimates of the state of nutrition made by experienced physicians.

In any discussion of malnutrition the studies of Strang and his associates<sup>80</sup> are of interest, for these investigators have evidence to indicate that the gastro-intestinal tracts of undernourished subjects are not inferior to those of normal persons and that the undernutrition of such persons is not the result of anomalies of metabolism. The rôle of diseases of the gastro-intestinal tract in interfering with adequate nutrition or, as it is sometimes called, in conditioning states of deficiency is being repeatedly emphasized as an important cause of such states of deficiency in the United States.

The influence of the recent economic depression in the nutritional state of the people in this and other countries probably will not be known for many years. One reason for this is the lack of suitable criteria of malnutrition, and another is that a generation in the life of man covers many years. A recent League of Nations Bulletin, "Nutrition and

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78 Magee, H. E., and others. Discussion on the Assessment of State of Nutrition, *Proc Roy Soc Med* **28** 713 (April) 1935.

79 Crawford, W. L. Physical Examination of the Child. Its Objects and Methods, *Illinois M J* **65** 49 (Jan) 1934.

80 Strang, J. M., and Evans, F. A. Undernutrition and Its Treatment by Adequate Diet, *Ann Int Med* **7** 45 (July) 1933.

Public Health,"<sup>81</sup> suggests that no country can claim that its population is satisfactorily fed. Poverty is mainly to blame, ignorance to a less extent. Significant in this respect is the fact that protective foods, richest in vitamins and minerals, are the most expensive and in all countries are beyond the means of the great masses of people. Burnet and Aykroyd, who made the report, allege that in Great Britain between 10 and 25 per cent of the population cannot afford a diet of the type and quality now known to be essential as a safeguard against malnutrition and disease. It is claimed that more than 22 per cent of children in the United States investigated up to 1924 showed symptoms of malnutrition. In answer, the chief medical officer of the ministry of health of Great Britain has stated that the nutrition of the people of his country is better than at any period of which there is record.

In a recent summary on the nutritional status of 4,500 children who were on relief in San Francisco, Geiger and Bailett<sup>82</sup> conclude that even on conservative interpretation of their observations it must be admitted that the nutritional status of children who have been on commissary relief compares favorably with that of a normal or even a more privileged group in the community. In the establishment of relief rations considerable attention must be paid to a variety of factors emphasized in an editorial comment in *The Journal of the American Medical Association*.<sup>83</sup> These include racial differences as well as national habits in relationship to the consumption of food and the lack of safety in trusting the individual to the guidance of his appetite alone in the selection of an adequate diet. A practical fact in regard to the diet of persons on relief is that mentioned by Sherman,<sup>84</sup> who pointed out that nutritional benefit comes from what one eats more than from lists of what one should eat.

#### VITAMINS

Interest in the vitamins in the past year has been directed principally toward their further chemical identification, their synthesis and the preparation of concentrates and crystals suitable for oral and parenteral administration. Progress has been made, also, in the direction of the relation of vitamins to infections and in studies of the quantitative requirements for some of the vitamins and their metabolic activity in the animal organism.

81 Nutrition and Public Health, London letter, J. A. M. A. **105** 728 (Aug. 31) 1935.

82 Geiger, J. C., and Barrett, P. S. Nutritional Survey of Four Thousand Five Hundred Children on Relief, Am. J. Pub. Health **25** 183 (Feb.) 1935.

83 Diet and Relief, editorial, J. A. M. A. **104** 320 (Jan. 26) 1935.

84 Sherman, H. C. Food and Health, New York, The Macmillan Company, 1934, p. 99.

*Vitamin A*—It seems clear that vitamin A is closely related to the yellow pigment carotene. Vitamin A is the primary alcoholic derivative produced by the symmetrical division into two parts of the beta-carotene molecule. Beta-carotene consists of two B ionone rings united by a series of conjugated double bonds. Attempts to synthesize vitamin A have been made but have proved unsuccessful. For purposes of administration, livers of fish, particularly of the halibut, act as the richest known source of this vitamin. Concentrates and crystalline forms of the vitamin have not been produced. The feeding of vitamin A is superior to the administration of carotene because the former is more rapidly absorbed, and in the presence of fever or diarrhea carotene is poorly absorbed.

The quantitative requirement of vitamin A is unknown. However, it is estimated by Salter<sup>85</sup> that the minimal average value expressed as carotene is 0.3 mg. daily. The difficulty in expressing in exact figures the requirement of any vitamin is realized when one considers the influences of absorption, storage and destruction and the variability in minimal and optimal levels of requirement.

Among the interesting studies of metabolism of vitamin A recently reported is that of Baumann, Rusing and Steenbock.<sup>86</sup> These workers demonstrated that 95 per cent of vitamin A in the organism is stored in the liver and the remainder in the kidneys and lungs. Apparently 20 per cent of ingested vitamin is stored in the liver. The speed of absorption is surprisingly great, for from three to six hours after administration the larger part of the assimilated vitamin is already stored in the liver. Most of the ingested vitamin is destroyed or inactivated in the bowel. It is also pointed out that it is easier to maintain than to replenish stores of vitamin A. In contrast with these findings, Drummond, Bell and Palmer<sup>87</sup> report almost complete absorption of vitamin A by a patient whose condition led to part of the content of the thoracic duct being diverted into the pleural cavities. It is of interest to note that the absorption of vitamin A in this case was much more satisfactory than that of carotene, this bears out previous experimental evidence. Both carotene and vitamin A appear to be present (in the chylous fluid) in colloidal form and closely associated with the highly dispersed fat.

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85 Salter, W. T. Quantitative Aspects of Vitamin Requirement, *J. Am. Dietet. A.* **10** 296 (Nov.) 1934.

86 Baumann, C. A., Rusing, Blanche M., and Steenbock, H. Fat-Soluble Vitamins. XLII The Absorption and Storage of A in the Rat, *J. Biol. Chem.* **107** 705 (Dec.) 1934.

87 Drummond, J. C., Bell, Muriel E., and Palmer, Elizabeth T. Observations on the Absorption of Carotene and Vitamin A, *Brit. M. J.* **1** 1208 (June 15) 1935.

In studies on the carotene and vitamin A content of the blood serum of man, Schneider and Widmann<sup>88</sup> have observed that these substances are present only in the serum and not in the corpuscles. The effect of age is interesting, since it was noted that with increasing age the carotene content of the serum increases, while the vitamin A content decreases. Some evidence of the situation of storage of vitamin A in the liver is presented by Lasch,<sup>89</sup> who has demonstrated that in experimental animals (rats and rabbits) fatal phosphorus poisoning does not alter the amount of vitamin A stored in the liver, this suggests that storage occurs principally in the reticulo-endothelial cells. The Kupffer cells are not apparently affected following the administration of phosphorus, whereas the hepatic parenchymal cells are badly damaged. The possibility that vitamin A activity may influence the metabolism of cholesterol as a result of its action on the liver is suggested by Lasch.<sup>90</sup> He noted an increase in the cholesterol of the serum after the administration of large doses of vitamin A. The elevation of the cholesterol content is attributable primarily to an increase of the cholesterol esters fraction, and this indicates, according to Lasch, a direct action on the regulatory function exerted by the liver on the metabolism of cholesterol.

The clinical and pathologic features of avitaminosis caused by a lack of vitamin A have been described on numerous occasions. A splendid review of this subject has been made by Sweet and K'ang,<sup>91</sup> who have had unusually large experience among the Chinese. The effects of deficiency of vitamin A on the gastro-intestinal tract are rarely emphasized. It is of interest to note that Richards<sup>92</sup> observed that the earliest macroscopic sign of lack of vitamin A in young rats is in the epithelial lining of the digestive tract. Inflammation of the duodenum, small intestines and cecum is frequent, and in the glandular portion of the stomach there may be pittings, hemorrhagic points and even ulceration.

Whether or not the effects of avitaminosis may persist over a long period despite a subsequent liberal intake of the vitamin is a matter of great practical importance. From his experimental studies Richards produces evidence that pathologic conditions attributable to deficiency

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88 Schneider, E, and Widmann, F. Carotene and Vitamin A Contents of Human Serum, *Klin Wchnschr* **14** 670 (May 11) 1935

89 Lasch, Fritz. Vitamin A Metabolism and Liver in Experimental Phosphorus Intoxication, *Klin Wchnschr* **14** 1070 (July 27) 1935

90 Lasch, Fritz. Action of Vitamin A on Serum Cholesterol of Human Subject, *Klin Wchnschr* **13** 1534 (Oct 27) 1934

91 Sweet, L. K., and K'ang, H. J. Clinical and Anatomic Study of Avitaminosis A Among the Chinese, *Am J Dis Child* **50** 699 (Sept) 1935

92 Richards, Marion B. The Role of Vitamin A in Nutrition, *Brit M J* **1** 99 (Jan 19) 1935



of vitamin A may persist several months after a normal diet has been resumed. The author comes to the conclusion, difficult of proof, that damage caused by insufficiency of vitamin A in early youth cannot afterward be made good by an adequate supply of the vitamin, and chronic ill health may result.

Perhaps the most interesting clinical problem relative to vitamin A is that in regard to its relation to renal lithiasis. It has been recognized for several years that in the albino rat on a diet deficient in vitamin A there develops keratinization of the epithelium of the renal pelvis, and frequently urinary calculi of the calcium phosphate type occur. The application of this knowledge to renal lithiasis of man has provoked a variety of comment. Joly<sup>93</sup> expresses the opinion that the hypothesis that the presence of stones is evidence of a deficiency disease (principally, if not exclusively, attributable to deficiency of vitamin A) is the most plausible and probable that as yet has been advanced. One of the chief exponents of this theory, Higgins,<sup>94</sup> offers evidence that the addition of vitamin A causes disintegration and solution of the calculi experimentally produced in rats, and he adds that an acid ash diet high in vitamins has produced a decrease in size or total disappearance of renal calculi of some patients. The opinion of many urologists is apparently similar to that of Keyser,<sup>95</sup> who holds that a general survey of the subject reveals points which cannot be reconciled with certain clinical facts. Final conclusions must await further clinical study concerning this interesting problem. A good summary of it is to be found in a recent report of the Council on Pharmacy and Chemistry of the American Medical Association.<sup>96</sup>

The relation of vitamin A to resistance to infection will be considered subsequently.

*The Vitamin B Complex*—Vitamin B<sub>1</sub>. Interest in vitamin B<sub>1</sub> has been concerned principally with the isolation of the vitamin in crystalline form, studies of its chemical composition and preparation of concentrates. In the past few years crystals with vitamin B<sub>1</sub> activity have been prepared by Kinnersley and his associates<sup>97</sup> in England, Williams<sup>98</sup> in

93 Joly, J. S. The Etiology of Stone, *J Urol* **32** 541 (Dec) 1934.

94 Higgins, C. C. Production and Solution of Urinary Calculi, *J A M A* **104** 1296 (April 13) 1935.

95 Keyser, L. D. Recurrent Urolithiasis. Etiologic Factors and Clinical Management, *J A M A* **104** 1299 (April 13) 1935.

96 Vitamin A and Urinary Lithiasis, report of the Council on Pharmacy and Chemistry, *J A M A* **105** 1983 (Dec 14) 1935.

97 Kinnersley, H. W., O'Brien, J. R., and Peters, R. A. LXXXI Crystalline Vitamin B<sub>1</sub>, *Biochem J* **29** 701 (March) 1935.

98 Williams, R. R. The Structure of Vitamin B, *I Am Chem Soc* **57** 229 (Jan) 1935.

America, Windaus, Tschesche and Ruhkopf<sup>99</sup> in Germany and Van Veen<sup>100</sup> in Batavia. Recent cooperative efforts lead one to the conclusion that there is no reason for questioning the view that vitamin B<sub>1</sub> has been isolated, although certain details have yet to be settled. The exact chemical structure has not been clearly established, but the vitamin consists of a single molecule, with a formula of C<sub>12</sub>H<sub>18</sub>O<sub>2</sub>N<sub>4</sub>S. Fortunately, the wide distribution of vitamin B<sub>1</sub> affords a ready supply, synthesis, which will be a difficult task according to Kendall,<sup>101</sup> is not necessary in order to provide an available source of its concentrates and crystals. The vitamin in crystalline form may be purchased on the market at the present time.

There has been no significant advance in the knowledge of the physiologic activity of vitamin B<sub>1</sub>, it appears to have the property of a co-enzyme-like substance intervening in the chain of reactions in the oxidation of carbohydrate. Studies of the vitamin B content of various organs in the experimental animal are of interest. Brodie and MacLeod<sup>102</sup> noted that the liver of the rat which was on a normal diet contained ten times as much vitamin B per gram of tissue as muscle contained. The kidney contained a half and the brain a third as much as did the liver. While the heart muscle contained a quantity equal to that of the liver, the blood, the spleen and the lung contained traces only.

Cowgill<sup>103</sup> has published a summary in monograph form of his extensive studies on the vitamin B requirement of man, in which he summarizes the three important variables determining the requirement of vitamin B, namely, (1) body weight, (2) total metabolism or calories and (3) maximal normal weight of the species. He presents a formula which is applicable in determining the vitamin B requirement of man. Salter suggests that the vitamin B requirement of man is probably 0.5 mg daily. This is a low estimate compared to that of Cowgill<sup>103</sup> and of Vorhaus, Williams and Waterman<sup>104</sup>.

Beriberi is recognized rarely in the United States, but whether less severe states of deficiency of vitamin B are common is a matter for

99 Windaus, Tschesche and Ruhkopf, quoted by Kinnersley, O'Brien and Peters<sup>97</sup>

100 Van Veen, quoted by Kinnersley, O'Brien and Peters<sup>97</sup>

101 Kendall, E. C. Vitamins from a Chemical Viewpoint, *M. Clin. North America* **19** 477 (Sept.) 1935

102 Brodie, Jessie B., and MacLeod, Florence L. Quantitative Experiments on the Occurrence of Vitamin B in Organs, *J. Nutrition* **10** 179 (Aug.) 1935

103 Cowgill, G. R. The Vitamin B Requirement of Man, New Haven, Conn., Yale University Press, 1934

104 Vorhaus, M. G., Williams, R. R., and Waterman, R. E. Studies on Crystalline Vitamin B<sub>1</sub>, *J. A. M. A.* **105** 1580 (Nov. 16) 1935

debate Recent studies of Vorhaus, Williams and Waterman are interesting in this respect, since these investigators had available for therapeutic use a crystalline preparation of vitamin B<sub>1</sub> They estimate the normal intake of B<sub>1</sub> for adult man to be 1 mg daily and express the opinion that the minimal therapeutic dose that can be relied on to abolish any accumulated deficit is 10 mg daily Studies of patients with diabetes to whom the crystalline product was administered indicated an increase in the tolerance for carbohydrate of just over 50 per cent of the patients Good results in the treatment of patients with a variety of forms of polyneuritis were observed, and the amelioration of associated symptoms, such as weakness, loss of appetite and paresthesia, far exceeded the relief of pain In a selected group of patients who had hypotonicity of the gastro-intestinal tract without apparent organic cause but who had associated anorexia, constipation and vague muscular pains, much symptomatic relief was obtained As a result of these studies, Vorhaus and his associates are inclined to believe that states of deficiency of vitamin B are far more frequent than previously has been thought

Elsom<sup>105</sup> has reported interesting studies of 2 patients with deficiency of vitamin B To one, for five months a diet was given which was moderately deficient in vitamin B, although adequate in every other known requirement, the other patient had beriberi While marked relief of some symptoms was obtained after the addition of vitamin B<sub>1</sub> and B<sub>2</sub>, residual symptoms, finally relieved by the administration of yeast, suggest that there are in the vitamin B complex factors of significance other than B<sub>1</sub> and B<sub>2</sub> The principal effects of the absence of vitamin B seemed to be on the gastro-intestinal tract and the nervous system Edema and macrocytic anemia may also occur and secondary effects on the circulatory system are not uncommon

Strauss<sup>106</sup> has reemphasized the importance of nutritional factors in the so-called "alcoholic" polyneuritis He noted improvement of all of the 10 patients who had this disease when they continued to take their customary amount of alcohol but also received diets high in vitamin content, with yeast or yeast products by mouth and vitamin B concentrates and liver extract parenterally

The use of concentrates of vitamin B<sub>1</sub> and the use of crystalline vitamin B<sub>1</sub> in cases of diabetes is considered in the section on metabolism

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105 Elsom, Katharine O Experimental Study of Clinical Vitamin B Deficiency, *J Clin Investigation* **14** 40 (Jan) 1935

106 Strauss, M B The Etiology of "Alcoholic" Polyneuritis, *Am J M Sc* **189** 378 (March) 1935

Vitamin B<sub>3</sub> Further evidence of the existence of Vitamin B<sub>3</sub> is presented by Waterman and Ammerman<sup>107</sup> The clinical significance of this apparent fraction of the vitamin B complex is unknown

Vitamin B<sub>4</sub> Gyorgy<sup>108</sup> reports that in the absence of this fraction there occur lesions of the nervous system, with disturbances in coordination and ataxia

Vitamin B<sub>6</sub> This subject is considered in the section on vitamin G

*Vitamin C*—Since the chemical identity of vitamin C has been established, interest in this vitamin has been directed principally toward studies of the metabolism of this substance in the animal organism and the effects of its administration in crystalline form

One of the most interesting phases of vitamin requirement is that which has to do with the levels of minimal and optimal intake and utilization King and Menten<sup>109</sup> have demonstrated the significance of this phenomenon in work with guinea-pigs fed vitamin C in abundant protective and subprotective quantities In animals with partial depletion without external signs of scurvy the time of survival was shortened about 50 per cent and loss of weight was severe King and Menten demonstrated that there is a wide zone of deficiency in vitamin C without the appearance of scurvy, wherein physiologic processes are subnormal and sensitivity of the animal to injury from bacterial toxins is increased Jungeblut and Zwemer<sup>110</sup> present evidence that diphtheria toxin is inactivated by vitamin C in vitro These and other works suggest a relationship between cevitamic acid and the process of immunity

Interest in the clinical significance of vitamin C has been increased in recent years because of the suggestion by Rinehart and his associates<sup>111</sup> that vitamin C is a specific etiologic factor in rheumatic fever Perry<sup>112</sup>

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107 Waterman, R E, and Ammerman, M Studies of Crystalline Vitamin B Effect of Graduated Doses on Pigeons, *J Nutrition* **10** 161 (Aug) 1935

108 Gyorgy, Paul LXXXVI Investigations on the Vitamin B<sub>2</sub> Complex I The Differentiation of Lactoflavin and the "Rat Antipellagra" Factor, *Biochem J* **29** 741 (March) 1935

109 King, C G, and Menten, M L Influence of Vitamin C Level upon Resistance to Diphtheria Toxin, Changes in Body Weight and Duration of Life, *J Nutrition* **10** 129 (Aug) 1935

110 Jungeblut, C W, and Zwemer, R L Inactivation of Diphtheria Toxin in Vivo and in Vitro by Crystalline Vitamin C (Ascorbic Acid), *Proc Soc Exper Biol & Med* **32** 1229 (May) 1935

111 Rinehart, J F, Conner, C L, and Mettier, S R Further Observations on Pathologic Similarities Between Experimental Scurvy Combined with Infection and Rheumatic Fever, *J Exper Med* **59** 97 (Jan) 1934

112 Perry, C B Rheumatic Heart Disease and Vitamin C, *Lancet* **2** 426 (Aug 24) 1935

and Faulkner,<sup>113</sup> as well as others, disagree with this conclusion. While both of the latter observers could find evidence suggesting mild degrees of deficiency of vitamin C in some cases, they did not believe it to be a significant factor, and in the experience of Faulkner the administration of vitamin C to patients who had rheumatic fever did not influence the course of the disease.

A relationship between vitamin C and the blood was suggested in 1934 by Piesnall,<sup>114</sup> who noted a reduced number of platelets and anemia in cases of deficiency of vitamin C. Minot<sup>115</sup> emphasizes the occurrence of a normocytic or slightly macrocytic anemia in persons with deficiency of vitamin C. Faulkner has noted a slight but definite reticulocyte response following the administration of large quantities of orange juice or crystalline vitamin C, roughly proportional to the severity of the infection presented by the patient.

The fundamental importance of vitamin C in the formation of normal intercellular substance has been demonstrated by Menkin and his associates<sup>116</sup>. The failure to form this substance with normal properties in the presence of deficiency of vitamin C may be the result of reduced cellular oxidation.

There has been much discussion in the past year about the validity of the test of capillary resistance as a measure of deficiency of vitamin C and consequently of the incidence of such deficiency. Dalldorf and Russell,<sup>117</sup> who advocated the use of the test, report further on their studies of the inmates of a county home. To 14 inmates, tests of whom indicated reduced capillary resistance, 100 mg. of cevitamic acid was given intravenously. All of them made a prompt and marked response in capillary resistance, and the increased resistance persisted for twenty-four hours. The observers suggest that the individual requirement of antiscorbutic foods may vary and that various persons may differ regarding the absorption and utilization of the vitamin. It seems reasonable to hope that in the future a more satisfactory method will be established as a measure of sufficiency of vitamin C. Such a method is desirable in

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113 Faulkner, J. M. The Effect of Administration of Vitamin C on the Reticulocytes in Certain Infectious Diseases. A Preliminary Report, *New England J. Med.* **213** 19 (July 4) 1935.

114 Piesnall, A. K. The Relation of Avitaminosis C to Blood Clotting, *J. Nutrition* **8** 69 (July) 1934.

115 Minot, G. R. The Anemias of Nutritional Deficiency. Etiology, Diagnosis, Treatments and Prevention, *J. A. M. A.* **105** 1176 (Oct. 12) 1935.

116 Menkin, Valy, Wolbach, S. B., and Menkin, Miriam F. Formation of Intercellular Substance by the Administration of Ascorbic Acid (Vitamin C) in Experimental Scorbutus, *Am. J. Path.* **10** 569 (Sept.) 1934.

117 Dalldorf, Gilbert, and Russell, Hollis. The Effect of Cevitamic Acid Injections on Capillary Resistance, *J. A. M. A.* **104** 1701 (May 11) 1935.

view of the variability of results with the test of capillary resistance Perry suggests such a method, which might be called a test of vitamin C tolerance. A measured amount of the vitamin is given, and its excretion in the urine is studied. By a person well supplied with vitamin large quantities of the ingested vitamin will be excreted in the urine, in which it can be estimated quantitatively. On the other hand, if there is a deficiency of vitamin C, the organism will utilize much of the ingested vitamin and but small quantities will be excreted in the urine. Since the estimation of vitamin C in the urine is relatively simple, this method may become the most accurate measure in the clinical investigation of deficiency of vitamin C.

The use of crystalline cevitic acid in the treatment of patients with infantile scurvy has proved effective, according to Abt and Epstein,<sup>118</sup> who noted that the blood of scorbutic infants was low in vitamin C. Treatment of hemorrhagic conditions with cevitic acid has been suggested. The results seem variable. Junghans<sup>119</sup> expresses the opinion that it is of value in the treatment of uterine bleeding of various types. The mechanism of its activity is unknown, although it may effect changes in the intercellular substance of the capillaries.

A practical point in the intravenous administration of cevitic acid is suggested by Anderson and Leake,<sup>120</sup> who noted that hemolysis of the erythrocytes may occur if the crystals are dissolved in distilled water. They recommend for intravenous use solutions of the sodium salt of cevitic acid approaching approximate isotonicity, that is, 1 per cent of the salt dissolved in physiologic solution of sodium chloride or 3 per cent dissolved in distilled water. If only the acid is available, it should be neutralized with half its weight of sodium bicarbonate (sterile) in physiologic solution of sodium chloride or water before it is injected.

*Vitamin G*—Ever since the demonstration that the original water-soluble vitamin B is composed of several separate fractions there has been much interest in the number, character and physiologic properties of the various components. A heat-stable, antidermatitic factor was called vitamin B<sub>2</sub> or G. One year ago it was stated in this review that vitamin G was chemically closely related to the pigment group of flavines. Since that time, work has appeared which suggests that vitamin G is in fact composed of two distinct constituents, one a flavine and the other a supplementary substance contained in yeast extract. The latter

118 Abt, A. F., and Epstein, I. M. Cevitic Acid (Ascorbic Acid) in the Treatment of Infantile Scurvy, *J. A. M. A.* **104** 634 (Feb. 23) 1935.

119 Junghans, E. Vitamin C in Treatment of Gynecologic Hemorrhages, *Klin. Wchnschr.* **14** 899 (June 22) 1935.

120 Anderson, H. H., and Leake, C. D. Hemolytic Action of Cevitic Acid (Ascorbic) Acid, *J. A. M. A.* **105** 1033 (Sept. 28) 1935.

appears identical with the "factor Y" of Chick, Copping and Edgar <sup>121</sup> and with Gyorgy's vitamin B<sub>6</sub>. Gyorgy <sup>122</sup> points out that neither lactoflavine nor vitamin B<sub>6</sub> alone has growth-promoting action, but together they do have this action, apparently the pellagra-preventing factor corresponds to the supplementary substance, or vitamin B<sub>6</sub>. Gyorgy expresses the opinion that Castle's extrinsic factor will be more closely related to lactoflavine than to the pellagra-preventing, or vitamin B<sub>6</sub>, factor. A distinct difference in the content of these two factors in certain foods is of further interest in showing their independent existence. Gyorgy points out that fish muscle is a rich source of the antipellagra factor (B<sub>6</sub>) but that it is practically devoid of lactoflavine, while egg, despite its high content of lactoflavine, is devoid of antipellagra activity. The chemical character of the B<sub>6</sub> fraction is unknown.

There is still much discussion concerning the etiology of pellagra. The importance of the so-called secondary pellagra, that is, pellagra occurring secondary to an initial gastro-intestinal disorder the causation of which is entirely unconnected with pellagra, is reemphasized by Simpson <sup>123</sup>.

Despite variability in opinion as to the etiology, the treatment of pellagra is chiefly dietary. The rapid strides which have been made in this respect are well illustrated by Spies <sup>124</sup> in his studies at the Lakeside Hospital in Cleveland. From 1926 to 1930, 54 per cent of 73 patients with pellagra died despite good hospital care. During the past five years Spies and his associates <sup>124b</sup> have been able to reduce the mortality in persons with severe pellagra to 5 per cent or less. For the treatment of early pellagra these observers suggest adequate rest, a diet of 4,000 calories or more daily, supplemented by from 10 to 20 Gm of good brewer's yeast or wheat germ in iced milk or eggnog several times daily, so that the patient receives from 75 to 100 Gm daily. If necessary, to this may be added parenteral injections of liver extract, from three to five doses of 20 cc daily. Tincture of opium (from 2 to 5 or 6 cc daily) may be used but it is not usually efficacious.

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121 Chick, Harriette Copping, Alice M., and Edgar, Constance E. LXXXIV The Water-Soluble B-Vitamins. IV The Components of Vitamin B<sub>2</sub>, *Biochem J* **29** 722 (March) 1935.

122 Gyorgy, Paul. LXXXVII Investigations on the Vitamin B<sub>2</sub> Complex. II The Distribution of Lactoflavin and of the "Pellagra-Preventing Factor" (Vitamin B<sub>6</sub>) in Natural Products of Animal Origin, *Biochem J* **29** 760 (March) 1935.

123 Simpson, S. L. Secondary Pellagra, *Quart J Med* **4** 191 (April) 1935.

124 Spies, T. D. (a) Medical Treatment of Pellagra, *J A M A* **104** 1377 (April 20) 1935, (b) Medical Treatment of Early Pellagra, *ibid* **105** 1028 (Sept 28) 1935.

*The Occurrence of Other Essential Foodstuffs*—It is not clearly established that all possible essential foodstuffs have been recognized. In fact, each year there is reported the discovery of new essential substances not included in the present list of vitamins or minerals. Some of these substances have been called vitamins to establish their indispensable character. Two unsaturated fatty acids, linoleic and linolenic, which are nutritionally essential, have been named vitamin F. In the past year the existence of another essential foodstuff has been suggested by the work of Dam,<sup>125</sup> who describes a deficiency disease resembling scurvy in chicks, but it is not prevented by cevitamic acid. It is believed that the hemorrhagic tendency in this disease is produced by the absence of a fat-soluble substance which is antihemorrhagic, which is neither vitamin A nor vitamin D and which Dam has called the *Koagulations Vitamin*, vitamin K. Hog liver and hemp seed are said to be the best sources, while cod liver oil is practically devoid of the substance.

*Vitamin Therapy*—The Council on Pharmacy and Chemistry of the American Medical Association<sup>126</sup> has published an interesting report, "Shotgun Vitamin Therapy," in which is pointed out the frequent lack of rationale in the use of many preparations now on the market which contain combinations of all or some of the vitamins, frequently combined with some mineral or minerals. The lack of necessity of administering such complex combinations for the maintenance of health when a well balanced diet is taken and the almost complete absence from the literature of evidence suggesting the value and safety of such preparations are emphasized. Until such evidence is presented, it seems safer to avoid the general use of such preparations.

A few studies have been made on the value of local applications of vitamins in promoting the healing of wounds. After examining the effect of such applications, Lauber<sup>127</sup> came to the conclusion that the local application of vitamin A produces no acceleration in the process of healing and may in fact retard it. The application of vitamins B and C seems to retard healing, whereas after the application of vitamin D in small doses there may be the slightest acceleration, and in large doses retardation, in healing. Although Lauber believes that the value of vitamin ointments is questionable, he found evidence that small doses of vitamin A given by mouth work most satisfactorily in accelerating healing of wounds.

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<sup>125</sup> Dam, Henrik. CLIV The Antihæmorrhagic Vitamin of the Chick, *Biochem J* **29** 1273 (June) 1935.

<sup>126</sup> Shotgun Vitamin Therapy, report of the Council on Pharmacy and Chemistry, *J A M A* **105** 1037 (Sept 28) 1935.

<sup>127</sup> Lauber, H J. Experimental Studies on Relations Between Vitamins and Healing of Wounds, *Beitr z klin Chir* **151** 565 (June 5) 1935.



## RELATION OF VITAMINS TO INFECTIONS

Perhaps nothing in regard to the vitamins engages the attention to such a degree as the so-called anti-infective power of certain vitamins. As previously emphasized, there is no evidence to suggest that vitamin A has any anti-infective power other than its ability to maintain in a good state the epithelial barriers of the organism. The crux of the situation will lie in the demonstration, or in the failure to demonstrate, that an amount of a vitamin in excess of that normally obtained by well nourished persons will further increase their resistance to infection. During the past year numerous papers have appeared supporting or denying the valuable effect of vitamin A in the treatment of the common cold and other infections. There is a suggestion in the work of Cameron<sup>128</sup> and of Shibley and Spies<sup>129</sup> that although excess quantities of vitamin A did not reduce the incidence of acute infection of the respiratory tract the average duration of such infections was somewhat reduced. In the observations reported by Cameron, carotene was apparently as effective as vitamin A.

Although vitamin A apparently lacks anti-infective power, except in maintaining a normal epithelial barrier, there is recent evidence to suggest that once the epithelial barrier of the organism has been overcome, vitamin C may increase the powers of resistance against infection.

The evidence produced by Jungblutt and Zwemer suggests that vitamin C bears a relationship to immunologic processes, since guinea-pigs well fortified with vitamin C were able to resist the effects of diphtheria toxin and in vitro diphtheria toxin was found to be inactivated by ascorbic acid. The clinical bearings of these observations are as yet uncertain. Although it is recognized that patients who have scurvy are more susceptible to infection than are normal persons, vitamin C has not been widely used as an anti-infective agent.

## VITAMIN D, CALCIUM AND PHOSPHORUS

Any discussion of recent advances in the knowledge of one of these factors must take into account all of them. As Bills<sup>130</sup> has well expressed it:

Confusion in this field is understandable when one contemplates the permutations and combinations which are possible in a system comprising several forms of calcium and phosphorus in the blood, a reservoir and depository of these

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128 Cameron, Hazel C. The Effect of Vitamin A upon Incidence and Severity of Colds Among Students, *J Am Dietet A* **11** 189 (Sept) 1935.

129 Shibley, G. S., and Spies, T. D. The Effect of Vitamin A on the Common Cold, *J A M A* **103** 2021 (Dec 29) 1934.

130 Bills, C. E. Physiology of the Sterols, Including Vitamin D, *Physiol Rev* **15** 1 (Jan) 1935.

elements in bone, a fluctuating intake and output of them in the diet and excretions, and a dumping place for them in the soft tissues—all under the influence of many factors besides the parathyroid glands and the several forms of Vit D. As for the hormones and the vitamin, which seem to be the major forces in the system, it is most satisfactory to regard them as acting together, complementing, supplementing, or opposing each other as the occasion demands.

*Vitamin D*—Chemically, this vitamin is closely related to ergosterol, but as yet it is not known what structural changes occur when inactivated ergosterol is changed to the active form by irradiation. It seems widely accepted that vitamin D may exist in several different chemical forms, and there is evidence that provitamin D activity is not limited to ergosterol. The Kochs<sup>131</sup> have produced evidence, for example, that cholesterol itself, or a modification of it produced by heat, by alkali or by both, also has provitamin D potency. Although vitamin D is widely distributed throughout the animal kingdom, it is abundant only in fish, and except for occasional amounts gained by eating such foods as fish or eggs, the vitamin must normally be obtained by exposure of the surface of the body to the sun (Bills). Vitamin D may enter the circulation by several routes, and its absorption through the skin is well recognized. Although a considerable quantity of ingested vitamin D appears in the feces, it is not known whether this is the result of failure of absorption or whether it is the result of absorption with subsequent reexcretion.

*Calcium and Phosphorus* (Summarized from Schmidt and Greenberg<sup>132</sup>)—Animal organisms are dependent for their supply of these elements on plants, which in turn derive their needs from the soil or, in the case of aquatic plants, from the surrounding water. For man, the principal sources of these elements are milk and its products, nuts, certain vegetables, particularly beans, eggs, cereals, and meat. The form in which calcium and phosphorus exist is determined in part by the acid or alkaline reaction of the food, but inorganic salts, particularly calcium phosphate, are the principal sources of supply. The absorption of phosphorus, which always occurs in biologic material in the oxidized forms, namely, as derivatives of phosphoric acid, is delayed in the gastrointestinal tract, so that in all probability much of the calcium is absorbed before most of the phosphoric acid is set free by a process of hydrolytic cleavage. The advantage of this provision is that otherwise a considerable amount of calcium phosphate would be formed, and this,

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<sup>131</sup> Koch, Elizabeth, and Koch, F. C. Fractionation Studies on Provitamin D, *Science* **82** 394 (Oct. 25) 1935.

<sup>132</sup> Schmidt, C. L. A., and Greenberg, D. M. Occurrence, Transport and Regulation of Calcium, Magnesium and Phosphorus in the Animal Organism, *Physiol. Rev.* **15** 297 (July) 1935.

having low solubility, probably would lead to decreased absorption of both elements

In the absorption of calcium and phosphorus from the intestine, hydrochloric acid is an extremely important but not indispensable factor as an agent for effecting solution of insoluble calcium phosphate by the formation of more soluble chlorides of calcium. The small intestine, and particularly the duodenum, is important in the absorption of calcium salts

The bulk of the calcium in the body exists in the skeleton, while phosphorus is present also widely distributed in the soft tissues and body fluids. Sherman<sup>84</sup> estimates that 1 Gm of calcium a day would include an ample margin of safety for the average person, while an average intake of from 1 to 1.2 Gm of phosphorus is a safe figure for the average man

Calcium and phosphorus exist in the blood stream in a variety of forms, which adds confusion to studies of the metabolism of these substances in normal persons and in persons with rickets, tetany and other diseases

McLean and Hastings<sup>133</sup> have commented on the fact that the total calcium content of the serum or plasma is nearly all accounted for as calcium ions and calcium bound to protein. While the total calcium content of the serum may fluctuate under normal conditions, especially in response to fluctuations in the concentration of the total protein content of the plasma, the diffusible or ionic calcium is normally maintained within a relatively narrow range by a process of physiologic regulation in which the parathyroid glands play a prominent rôle. Approximately 50 per cent of the calcium content of the serum exists in the ionic or diffusible form, which is the fraction of primary physiologic importance

While it is clearly recognized that calcium, phosphorus, vitamin D and parathyroid hormone are essential for the mineralization of normal bone and probably play a rôle in the development of rickets and certain other diseases, the rôles played by each individual factor and their interrelationships are not clearly understood. The activity of vitamin D in this respect has been stated to be in the retention of calcium and phosphorus in the body as a whole, in the deposition of calcium and phosphorus in the bones and perhaps in the concentration of these elements in the blood. Early workers in this field suggested that vitamin D in some manner regulates the passage of calcium and phosphorus through the intestinal wall and that therapeutic doses of the vitamin increase the absorption of calcium and phosphorus. Another possible

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133 McLean, F. C., and Hastings, A. B. Clinical Estimation and Significance of Calcium-Ion Concentrations in Blood, *Am J M Sc* **189** 601 (May) 1935

explanation of the retention of calcium and phosphorus which occurs during the administration of vitamin D is the decreased excretion of these elements through the intestinal wall or kidney. The rôle of vitamin D in the deposition of calcium and phosphorus in bone is also uncertain, but it is clearly recognized that in the absence of vitamin D bone is abnormal both in chemical composition and histologic structure. It is possible that some of these metabolic factors are influenced by vitamin D, which may perhaps be called the regulator of the level of calcium in the blood, through stimulation of the parathyroid glands or by rendering the organism more responsive to the hormone.

In this connection the studies of Wilder, Higgins and Sheard<sup>134</sup> are of particular interest, for the authors have demonstrated in the chick that deprivation of vitamin D insufficient in degree to cause rickets will produce hypertrophy and hyperplasia of the parathyroid glands. Other observations that these investigators made are interpreted to mean that the supply of parathyroid hormone determines the sensitivity of the organism to the action of vitamin D. A diminished supply of the hormone, such as may be available after parathyroidectomy, diminishes the ability of the organism to function normally with restricted amounts of D. An augmented supply conditions the tissues of the organisms so that the effects of the vitamin are more intense and so that amounts of vitamin which otherwise would not prevent rickets do prevent it.

The rôle of concentration of calcium and phosphorus in the blood in the mineralization of bone and the part played by vitamin D in such concentration in rickets is questionable. As a result of their recent studies, Compere, McLean and Hastings<sup>135</sup> report that neither the amount nor the state of calcium in the blood serum of rachitic infants is necessarily altered from that in the serum of normal infants. They express the belief, therefore, that the pathologic change in patients with rickets is not on the basis of a change in the amount or state of the calcium in the blood. The effect of vitamin D in increasing the phosphorus content of the serum in patients with rickets may come about as a result of increasing the capacity of the blood to hold phosphorus, possibly by raising the level at which it begins to be excreted.

The immediate rôle of calcium and phosphorus in relation to these metabolic processes is probably more simple than that of vitamin D. In the absence of sufficient quantities of either calcium or phosphorus,

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134 Wilder, R. M., Higgins, G. M., and Sheard, Charles. The Significance of the Hypertrophy and Hyperplasia of the Parathyroid Glands in Rickets and Osteomalacia, *Ann Int Med* 7 1059 (March) 1934.

135 Compere, E. T., McLean, F. C., and Hastings, A. B. State of Calcium in the Fluids of the Body. II. Calcium in the Blood in Rickets, *Am J Dis Child* 50 77 (July) 1935.

and particularly calcium in assimilable forms, rickets or other abnormality of bone may develop despite an adequate intake of vitamin D and the presence of normal parathyroid glands. As Schmidt and Greenberg point out, the composition of the blood with respect to the calcium and phosphorus, in the last analysis must depend on a balance of their absorption from the ingested food, their excretion by way of the urine and feces and their storage and release from the tissues, more particularly the skeleton.

In the past year certain other observations have been made in regard to the calcium and phosphorus content of the blood and vitamin D, which are worthy of separate report. McLcan and Hastings have attempted to simplify interpretations of estimations of serum calcium and diffusible and nondiffusible forms. They express the belief that increases in the concentration of the calcium ion are presumptive evidence of hyperparathyroidism. Decreases in the concentration of the calcium ion occur only as a result of hypofunction of the parathyroid glands or as a result of the hypophosphatemia of uremia. The possible exceptions to these two conclusions may be hypercalcemia from the administration of viosterol in excessive doses and so-called low-calcium rickets, associated with infantile tetany.

Problems in the assimilation and utilization of calcium are presented by Telfer (according to Friedman<sup>136</sup>) and by Kohman and Sanborn<sup>136b</sup>. Telfer points out the interesting fact that the amount of calcium retained by infants who receive whole cow's milk is two or three times greater than that retained by normal infants fed breast milk. Why under such circumstances rickets is more common among bottle-fed babies is uncertain. Kohman and Sanborn have studied the effect of the oxalic acid content of leafy vegetables on the assimilation of calcium. While there is insufficient oxalic acid in these foods to produce toxic effects, the formation of highly insoluble calcium oxalate may interfere with absorption, and oxalate may also interfere with the retention of calcium.

To certain patients who fail properly to absorb lipid, vitamin D may be administered by the dermal route. The vitamin is satisfactorily absorbed from the skin, and when administered in this fashion it will cure or prevent rickets of experimental animals. Since dermal absorption is variable, the dose required is not clear.

*Toxic Effects of Vitamin D*—While there is as yet little information in regard to the quantitative requirements of the vitamins, much

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136 Telfer, quoted by Friedman, Samuel. Infant Feeding and Nutrition, *Am J Dis Child* **49** 460 (Feb) 1935.

136b Kohman, E F, and Sanborn, N H, cited in Oxalic Acid and Calcium Utilization, editorial, *J A M A* **105** 440 (Aug 10) 1935.

interest has been aroused over the effects of excessive quantities of them. As emphasized last year, there is not good evidence of such toxic effects except in the case of vitamin D. Much interest has attached itself to this problem in view of the almost universal use among civilized people of various preparations of vitamin D in the treatment of infants and children. Bills has recently reviewed the evidence on this point and has emphasized the fact that the range between the ordinary therapeutic doses of vitamin D and the dose which produces adverse symptoms is extraordinarily wide. This is fortunate, because probably no potent substance enters the bodies of animals in more variable amounts than does vitamin D. Bills suggests that the production of toxic effects depends on the daily dose, the duration and the route of administration, the calcium and phosphorus content of the diet, the age and activity of the subject, the individual susceptibility, the susceptibility of the species and other factors. The lethal dose of vitamin D for man is unknown. Reed's<sup>137</sup> daily dose given to patients who had hay fever amounted to about 2,760,000 international units (equivalent in rat units to 30 liters of cod liver oil). While this dosage caused some patients to have unpleasant symptoms, there were no serious effects. When Spies and Hanzel<sup>138</sup> administered more than 18,000,000 international units daily, hypercalcemia was produced, but pathologic calcification of the tissues was not observed.

Bills lists the following warning symptoms of toxic action of vitamin D: a sense of well-being and increased appetite changing to nausea, anorexia, vomiting, cramps, diarrhea, frequent urination, sometimes neuralgia along the course of the mandibular branch of the trigeminal nerves, tenderness of the teeth and gums, pain in the muscles and joints, dizziness, muscular weakness, headache and haziness of memory.

#### DENTAL CARIES

Great interest has been displayed in recent years in the dependence of normal development of the teeth on adequate nutrition and in the relationship between dietary deficiency and dental caries. Since dental caries is found predominantly among civilized peoples, much study has been given to the dietary differences which exist between civilized and uncivilized peoples. Discovery of the vitamins and of the importance of calcium and phosphorus has precipitated such investigations and has added much information about normal dentition which should be of

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<sup>137</sup> Reed, C. I. Symptoms of Viosterol Overdosage in Human Subjects, *J. A. M. A.* **102** 1745 (May 26) 1934.

<sup>138</sup> Spies, T. D., and Hanzel, R. F. Experimental Production of Hypercalcemia in Human Beings by Means of Irradiated Ergosterol, *Proc. Soc. Exper. Biol. & Med.* **31** 747, 1934.

great value in the prophylaxis of dental caries. That caries is a matter of great importance from the standpoint of public, as well as of individual, health is well illustrated by the fact that a survey made in 1934 by the British Dental Association<sup>139</sup> revealed that of 3,000,000 children, 60 per cent had defective teeth and needed treatment.

At present there are two schools of thought in the study of dental caries. According to Bunting,<sup>140</sup> the first school holds the view that the most important consideration is the environment of the teeth (bacterial flora, carbohydrates, acids formed in the mouth and films and plaques over the teeth which may protect the acids of caries from dilution and neutralization). The second school contends that the perfection of the tooth itself and its resistance to the attacking force are most important. Both groups agree that diet is closely associated with dental caries and that at present the most efficient known preventive measures against dental disease are dietary.

The various factors in diet which have been considered important in dental caries include calcium, phosphorus, carbohydrate and vitamins A, C and D. It is recognized also that the mechanical state of the food is significant. As one cause for confusion in this problem, Schmidt and Greenberg point out that too much emphasis has been placed on the metabolism of each individual element rather than consideration to the subject in its entirety. Nevertheless, brief discussion will be given to the rôle played by the mentioned factors.

*Calcium and Phosphorus*—Since 97 per cent of the inorganic salts found in enamel and 62 per cent of those found in dentin are made up principally of calcium phosphate, it is obvious that these elements are essential in the development of normal teeth. However, numerous studies indicate that a deficiency of calcium and phosphorus is not of any moment in determining hypoplasia of the enamel or increased susceptibility to caries. The work of Boyd, Drain and Stearns<sup>141</sup> on the retention of calcium and phosphorus showed that the highest retention of calcium and phosphorus was noted among children whose teeth gave evidence of inactive decay and that the least retention was found among those who gave evidence of active caries. Retention among those children who had no caries averaged approximately 50 per cent higher than among those who had active caries, despite the fact that among the latter retention was as high as, or higher than, that usually accepted as normal.

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139 The Prevalence of Dental Disease, London letter, J. A. M. A. **104** 2277 (June 22) 1935.

140 Bunting, R. W. Diet and Dental Caries, J. Am. Dent. A. **22** 114 (Jan) 1935.

141 Boyd, J. D., Drain, C. L., and Stearns, Genevieve. Metabolic Studies of Children with Dental Caries, J. Biol. Chem. **103** 327 (Dec.) 1933.

*Carbohydrate*—The rôle of carbohydrates in the production of dental caries is highly disputed. Some investigators are of the opinion that a diet high in carbohydrate, leading to marked increase in the *Bacillus acidophilus* content of the saliva, is a factor of great significance in the development of dental caries. Bunting suggests that thus far between persons free from caries and persons susceptible to caries the only observed differential characteristic offering a high degree of correlation is the relative number of *B. acidophilus* organisms in the mouth. Those who belong to the group who believe in the theory that the perfection and resistance of the tooth itself are the most important factors in resisting dental caries are under the impression that the rôle of bacteria in the control of caries seems to be secondary. Consequently, if the diet is adequate in those substances which are required in normal nutrition, caries will be controlled or arrested. Bunting summarizes the problem by saying that the manner in which, and the extent to which, sugar enters into the problem of dental caries is not as yet apparent.

*Vitamin A*—Vitamin A is not clearly an essential for normal dental development. May Mellanby<sup>142</sup> is of the opinion that this vitamin is significant in the development of the gingival epithelium and that deficiency of this factor may therefore favor the development of pyorrhea.

*Vitamin C*—The importance of vitamin C in dental caries was first emphasized by Howe<sup>143</sup>. It has been demonstrated that changes in the teeth of guinea-pigs occur at an early stage of deficiency of vitamin C and afford the surest clinical sign of scurvy in its latent stages. Hanke<sup>144</sup> produces evidence to suggest that a pint of orange juice should be taken every day to provide adequate amounts of vitamin C in preventing and healing dental caries, but against this is a wide variety of carefully collected clinical observations. The immediate rôle of vitamin C in dental development is in the maintenance of normal functional activity and prevention of premature degeneration of odontoblasts and cementoblasts.

*Vitamin D*—To the Mellanbys<sup>145</sup> must go credit for emphasizing the rôle of vitamin D in dental caries. In their opinion it is the most

142 Mellanby, May. Diet and the Teeth. An Experimental Study. II. A Diet and Dental Disease, B. Diet and Dental Structure in Mammals Other Than the Dog, Medical Research Council, Special Report Series, no. 153, London, His Majesty's Stationery Office, 1930.

143 Howe, P. R. Investigations of Dental Caries, *J. Am. Dent. A.* **14** 1864 (Oct.) 1927.

144 Hanke, M. T. The Role of Diet in the Cause, Prevention and Cure of Dental Disease, *J. Nutrition* **3** 433 (Jan.) 1931.

145 Mellanby, Edward. Nutrition and Disease. The Interaction of Clinical and Experimental Work, London, Oliver & Boyd, 1934. Mellanby<sup>142</sup>.



important protective factor available in the diet. Much controversy still exists in regard to the indispensability of vitamin D in the prevention and healing of dental caries. The frequent lack of relationship between caries and rickets is emphasized in this connection. Others<sup>146</sup> have produced evidence that dental caries may exist although there is no lack of vitamin D during the development of teeth and that decay may continue although large doses of vitamin D are being administered. The rôle of vitamin D, calcium and phosphorus in relation to dental development will be considered in the paragraphs on rickets.

*Fineness and Coarseness of Food*—Hoppert, Webber and Canniff<sup>147</sup> have demonstrated that fineness of division of food is more important than quality in the production of dental caries of rats. They were able to produce caries at will by feeding adequate diets of food coarsely ground which did not produce caries when the food was finely ground.

In summarizing, Bunting states: "(1) In a small percentage of cases, inherited tendencies or inherent characteristics may be more important factors in caries susceptibility than any ordinary dietary consideration. (2) In the majority of cases dental caries will be definitely arrested by the adoption of a simple, fairly adequate, low sugar diet. (3) No constant relationship could be found between the degree of activity of dental caries and the amounts of calcium phosphorus, vitamin D or C, or the acid base value in the diet, or in the blood or saliva." It is of interest to note that while Bunting expresses the opinion that diet controls dental caries through determination of the environment of the teeth and Drain and Boyd<sup>148</sup> are firmly convinced that endogenous factors are responsible primarily for the control and the arrest of dental caries, nevertheless the diets advised by these two opposing groups are essentially the same. A sample diet (Drain and Boyd) for a child from 5 to 16 years of age would consist of 1 quart (946 cc) of milk, at least one egg, one serving of meat, fish, chicken or liver, two vegetables, one-half cup of each, one orange, apple or tomato and one additional fruit, 1 teaspoonful of cod liver oil, and 6 teaspoonfuls of butter. Large quantities of sugar are better omitted.

#### IRON AND COPPER

Perhaps the most interesting report in relation to hemoglobin and iron metabolism during the past year is that of Whipple,<sup>149</sup> in his Nobel

146 Hansman, F. S., and Marshall, F. The Etiology of Dental Caries, *M J Australia* **2** 511 (Oct. 20) 1934.

147 Hoppert, C. A., Webber, P. A., and Canniff, T. L. Production of Dental Caries in Rats Fed an Adequate Diet, *J Dent Research* **12** 161 (Feb.) 1932.

148 Drain, C. L., and Boyd, J. D. Endogenous Factors in the Control and Arrest of Dental Caries, *J Am Dietet A* **10** 471 (March) 1935.

149 Whipple, G. H. Hemoglobin Regeneration as Influenced by Diet and Other Factors, *J A M A* **104** 791 (March 9) 1935.

prize lecture, entitled "Hemoglobin Regeneration As Influenced by Diet and Other Factors" In this report he summarizes the experience of his colleagues and himself in demonstrating the value of various factors in the regeneration of hemoglobin of dogs rendered anemic at constant levels by suitable removal of new-formed hemoglobin Liver stands out as the most potent dietary factor, with kidney a close second and thereafter gizzard, spleen and pancreas Iron was found to be the most potent inorganic element The potency of human liver compared with that of standard animal liver was of interest That of young, healthy adults obtained at necropsy gave average values of 160 per cent (compared with those of pig liver, 100 per cent) Liver tissue from elderly persons who had arteriosclerosis and degenerative changes gave a value of 117 per cent That of persons with chronic infections and cirrhosis gave about normal values except when hepatic insufficiency intervened, then the values fell to 48 per cent (one-third that of normal human liver) In persons with pernicious and aplastic anemia the values ran to more than 200 per cent

The dependence of anemia of man on nutritional deficiency is emphasized by Minot He points out that there are three classes of dietary substance the lack of which leads to anemia 1 Lack of iron leads to the formation of microcytic and hypochromic erythrocytes 2 Lack of vitamin C leads to the formation of normocytic or slightly macrocytic erythrocytes 3 A mysterious substance is contained abundantly in liver, the absence of which leads to pernicious anemia From the clinical standpoint, Minot calls attention to the rôle which may be played by infection, increased or altered metabolism, arteriosclerosis or serious damage to vital organs in precipitating the person who is receiving "just enough" iron into one of the states of anemia mentioned

There has always been much discussion of the requirement of iron by the normal adult and the effect of insufficient quantities of iron on the development of anemia In the past few years the availability of iron which occurs in foods has been shown to be of great significance Recent studies by Farrar and Goldhamer,<sup>150</sup> if confirmed, may force a revision of some conceptions in regard to the requirement of this element During a study of balance carried out on a man over a longer period of time than usual, these workers were able to maintain the iron balance with an intake of 4.9 mg daily, and the blood, that is, the hemoglobin and iron content and the erythrocyte count, remained normal during the time over which the mentioned intake was continued The authors are inclined to the opinion that the iron requirement of the

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150 Farrar, G. E., Jr., and Goldhamer, S. M. The Iron Requirement of the Normal Human Adult, *J. Nutrition* **10**:241 (Sept. 10) 1935

normal man is not more than 5 mg daily. The normal excretion of iron in the urine was found to amount to 0.02 mg for each 100 cc.

An exceedingly important conception is that which Elvehjem, Hart and Sherman<sup>151</sup> present on the availability of iron in many foods, that is, the proportion of the total iron content of a food which the gastrointestinal tract and the organism are able to utilize. Naturally, the amount of available iron is more important than the total iron content of the diet. Hematin iron apparently is not utilized by the digestive tract. In the aforementioned studies of balance of Farrar and Goldhamer, of the 5 mg of iron given daily, only 3 mg was in the available form.

Some very interesting studies of nutritional anemia have been reported in the past year. Results of scientific studies are rapidly revising ideas in regard to the etiology and treatment of this exceedingly common condition in infancy. Davidson, Fullerton and Campbell<sup>152</sup> report that this type of anemia is of relatively infrequent occurrence and of minor clinical importance (except at two age periods in infants between the eleventh and the twenty-third month of life and among women). In women pregnancy and menstruation are probably significant contributing etiologic factors. In their studies of 3,500 persons in Aberdeen these investigators found anemia in the following groups: 41 per cent of infants less than 2 years of age, 32 per cent of children of school age, 2 per cent of school children and 45 per cent of women.

While the normal full term infant is usually born with large stores of iron, the premature baby is frequently anemic. The main mechanisms which may be concerned in the development of the anemia of prematurity are said to be deficient antenatal storage of iron or possibly of copper or of some other essential hematogenic substance, and perhaps deficient formation of blood attributable to hyperplasia of marrow or to increased destruction of blood. According to editorial comment in *The Journal of the American Medical Association*,<sup>153</sup> most evidence favors the latter view, although it is not certain.

In the treatment of nutritional anemia, which is a normal phenomenon in infancy, Usher, McDermot and Lozinski<sup>154</sup> report that the

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151 Elvehjem, C. A., Hart, E. B., and Sherman, H. C. The Availability of Iron from Different Sources for Hemoglobin Formation, *J. Biol. Chem.* **103** 61 (Nov.) 1933.

152 Davidson, L. S. P., Fullerton, H. W., and Campbell, R. M. Nutritional Iron-Deficiency Anemia, with Special Reference to Prevalence and Age and Sex Incidence, *Brit. M. J.* **2** 195 (Aug. 3) 1935.

153 Anemia of Premature Infants, editorial, *J. A. M. A.* **104** 565 (Feb. 16) 1935.

154 Usher, S. J., MacDermot, P. N., and Lozinski, E. Prophylaxis of Simple Anemia in Infancy with Iron and Copper. Effect on Hemoglobin, Weight and Resistance to Infection, *Am. J. Dis. Child.* **49** 642 (March) 1935.

addition of fruit, vegetables and cereals is not a preventive factor and that the administration of iron in doses of 1.5 to 3 Gm daily was not as effective as when the iron was combined with from 1/60 to 1/32 gram (0.0011 to 0.002 Gm) of copper daily. It was also observed that infants so treated with iron and copper had a definite advantage in lessened incidence and severity of infection as well as in a lower mortality. Mackay<sup>155</sup> reports similar but more striking results.

Although it is difficult to demonstrate the rôle of copper in forms of anemia other than the nutritional variety, copper apparently plays an essential rôle in the formation of hemoglobin. Chou and Adolph's<sup>156</sup> studies on copper balance showed the copper requirement of man to be about 2 mg daily. This element, which is excreted chiefly in the feces, also appears in the urine at fairly constant levels (average, 0.25 mg daily). Copper, which occurs in the blood in larger than normal quantities in many forms of anemia, is stored principally in the liver, muscle and bones.

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155 Mackay, Helen M. M., quoted by Usher, MacDermot and Lozinski<sup>154</sup>

156 Chou, T. P., and Adolph, W. H. LIV Copper Metabolism in Man, *Biochem J* **29** 476 (Feb.) 1935

## Book Reviews

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**Working Test as a Clinical Method for Determining the Function of the Lungs** An Investigation in Cases of Tuberculous Changes Especially in Collapse Therapy By I L Bluhm Supplement LXV, Acta Medica Scandinavica Pp 209, with 5 illustrations and 78 tables Stockholm P A Norstedt & Soner, 1935

As a preliminary to his main work Bluhm has investigated the basal metabolism and the minute volume of cardiac output in tuberculous patients. The body of the report deals with a functional test of the lungs and a comparison with readings for vital capacity in the same cases. The history, technic and material are discussed under each heading. Brief histories of all the patients are given, and results are tabulated in detail and with numerous charts.

In determination of the standard metabolism, the oxygen consumption was measured with Krogh's apparatus and converted by use of the tables of Harris and Benedict, using plus 15 per cent as the upper limit of normal. In 40 ten minute and 411 five minute tests on a variety of tuberculous patients, some under treatment by different types of collapse therapy, Bluhm found a normal standard metabolism independent of the activity, the extension and the clinical nature of the process. In 36 cases no parallelism was found between the basal metabolic rate and the sedimentation reaction. Even in cases in which minor elevations of temperature were present, the standard metabolism was normal.

The minute volume of cardiac output was determined by the acetylene method of Grollman on 35 tuberculous patients, 20 of whom had some degree of collapse of the lung. In all the patients except 1 with severe pulmonary changes normal values were found for minute volume, utilization and stroke volume. Bluhm found the method not applicable in cases in which the vital capacity was 1.5 liters or less.

The study of the function in tuberculous lungs was made by the following method, which has been used by Nylén in cardiac diseases. A five minute curve of oxygen consumption is obtained under standard conditions. Immediately following the patient starts walking up and down three sets of stairs (three steps up and three steps down in each set) arranged in a circle, at a rate of eighty-eight steps per minute paced by a metronome. After twenty rounds (occasionally only ten rounds when the patient became easily short of breath) he reclines on a sofa, and forty-five seconds after the cessation of work a second curve of oxygen consumption is started and continued for four minutes. The percentage increase in oxygen consumption per minute after work is calculated and referred to as the relative oxygen debt. In 67 tests on 31 normal persons the relative oxygen debt was practically always between 10 and 25 per cent for either ten or twenty rounds. The maximum variation in repeated tests on the same subject was 6 per cent. The test was applied to 102 tuberculous patients mostly between the ages of 20 and 30. A total of 411 tests were made. A relative oxygen debt of more than 25 per cent is considered abnormal, and the term respiratory insufficiency is used to describe the condition in cases in which such values obtain. Eight of 43 patients without operative intervention showed respiratory insufficiency which could be explained usually by the extent of the pulmonary lesions. Tests were made on patients under pneumothorax treatment before and after a refill with nitrogen gas. In 10 of 32 tests there was an increased relative oxygen debt. The increase was dependent on the degree of respiratory insufficiency present and the amount of gas injected. There were no increased values in cases in which the relative oxygen debt was below 35 per cent before a refill, even when 800 cc of gas was added. Usually by the second, and practically always by the third, morning after the refill the values had returned to those present before insufflation.

Of 43 patients with unilateral pneumothorax, 33 showed a relative oxygen debt above 25 per cent. In all cases in which collapse was effective there was an increase in the relative oxygen debt following the induction of pneumothorax. The degree of respiratory insufficiency was dependent on the degree of collapse and the type and extent of the original tuberculous process. The following tendencies were noted on smaller groups of patients. There was a greater degree of respiratory insufficiency in cases of unilateral pneumothorax in which the other lung had previously been treated with gas than in simple unilateral pneumothorax. In seropneumothorax the change in the relative oxygen debt is dependent on an increase or a decrease in the amount of exudate, other factors being the same.

A comparison of vital capacity and relative oxygen debt is made. In general, there is an abnormal decrease in vital capacity in cases in which there is an abnormal increase in the relative oxygen debt. However, Bluhm believes that there is more individual variation in readings for vital capacity and that the increased value of the relative oxygen debt is more sensitive as an indicator of the type of condition which causes clinical dyspnea. One senses that he regards vital capacity more as an anatomic measure and relative oxygen debt more as a physiologic measure of respiratory function.

An attempt is made to correlate the present working capacity of the patients and the findings of the relative oxygen debt. There may be some doubt as to the final value of such comparison, in view of the relatively short time which has elapsed, the difficulty of evaluating working capacity and the uncertainty of the course of pulmonary tuberculosis. However, Bluhm thinks that there is good correspondence between the results of the functional test and the present working capacity of the patients, even if one ignores the clinical changes.

A large amount of work is represented in this investigation, and one feels that the conclusions are in the main fairly drawn. As to the possible clinical application of the method, it would be difficult to make a forecast. The procedure would seem to offer an objective measure of the tendencies which express themselves clinically by the development of dyspnea.

**Ueber Sternalpunktionen** By Elsa Segerdahl. Acta Medica Scandinavica, Supplementum LXIV. Pp 162, with 16 illustrations. Uppsala: Appelbergs Boktryckeriaktiebolag, 1935.

This monograph presents a thorough and extensive investigation of the aspiration method (Arinkin) of obtaining bone marrow for biopsy. The literature is thoroughly reviewed. The experiments of other investigators were painstakingly repeated. One hundred and ten normal persons and seventy-five persons with pathologic conditions were studied.

The simplicity of this technic commends itself for clinical use (an article describing an almost identical technic of bone marrow puncture appeared in a recent issue of the ARCHIVES OF INTERNAL MEDICINE 55 186 [Feb.] 1935). The loss of structural relationships in the marrow so removed is the only limitation of the method that does not apply to other methods of obtaining marrow for biopsy. In this method, as in others, there is an indeterminable admixture of peripheral blood and specific bone marrow elements. Segerdahl confirms the findings of Tuschinsky and Kotlarenko that the greater the amount of material aspirated the greater the dilution with blood. The withdrawal of 0.2 cc. of material is recommended.

Differential counts of the aspirated material are of questionable value, as the variability is too great. The findings of an unusually high or low cell count (from 70,000 to 80,000 per cubic millimeter was the average leukocyte count) or of diseased cells are of greater significance.

Aleukemic leukemia was the only condition in which the method was found to be of distinct diagnostic value. During severe remissions in cases of pernicious anemia a characteristic and diagnostic increase in megaloblasts in the marrow was found. However, the method is of no value in mild remissions or in patients

treated with liver Segerdahl points out that a change from a megaloblastic marrow to a normoblastic marrow begins within twenty-four hours after the institution of the parenteral administration of liver Therefore the potency of a liver preparation may be judged more rapidly by this method than by any other The criterion, however, is purely qualitative

**The Principles and Practice of Medicine** By Sir William Osler Twelfth edition Revised by Thomas McCrae Price, \$8.50 Pp 1196, with 22 illustrations New York D Appleton-Century Company, Inc, 1935

"The Principles and Practice of Medicine" of Sir William Osler, the textbook for medicine used in the instruction of nearly all today's practitioners when they were students, has been continuously revised and recedited since the death of Osler by his former associate, Thomas McCrae The reviewer, as he scans these pages, is reminded vividly of the copy of that earlier edition, read through more than once, forward and backward, in preparation for those recitations and examinations that then seemed so richly pregnant with distressing possibilities The fresh clean pages of this new book contrast strangely with those of the old They were covered with marginal notes of the gems of wisdom that fell from the lips of the old professors They were illuminated also with red lines which underscored those passages intended to be stamped indelibly on the memory and by occasional puns or raw anatomic jokes and pictures, here and there, of this or that outstanding and usually peculiar character of some classmate or teacher These pages are fresh and new, but what is more to the point, they are completely up to date

The style of the old master has been retained remarkably—the opening chapter on typhoid fever is very little changed from what it was when Osler wrote it, but what a lot of information has been added! New diseases appear, some grow less important, while others disappear, as is written by McCrae in his interesting preface There are changes and additions in this last revision in practically every part of the book Certain sections are new or have been altered materially A long list of these is given, among them are the divisions on undulant fever, psittacosis, hypoglycemia, agranulocytosis and fifty others

There is much to be said for a textbook of medicine written, as is this, by a single author The number of physicians today who are qualified to attempt such a task is small, and yet it is true, as is stated by McCrae, that the splitting of internal medicine into separate compartments tends to emphasize the study of one part without sufficient attention to the fact that patients are individuals and are made up of many systems "Too often the idea is held that a clinician can be made

with the aid of instruments and laboratory procedures Time, effort, and hard work must go to the acquiring of a knowledge of disease We cannot be Osler's, but we can do our best to follow his footsteps" The physician and student should learn everything possible about the patient by the use of his senses and brains before turning to the laboratory, and, so far as possible, a textbook of medicine should emphasize the clinical side of the problems of disease This policy has been followed conscientiously in the preparation of the successive editions of the Osler text

**Tuberculosis** By Dr Fred G Holmes Price, \$2 Pp 312 D Appleton-Century Company, Inc, 1935

This volume is a valuable addition to the list of books that are designed as guides for patients suffering from pulmonary tuberculosis It is written by one who is recognized as an authority and epitomizes his long clinical experience in the diagnosis and treatment of tuberculosis It is comprehensive enough to cover all the important subjects on which the patient requires information during the long course of his illness and is written with such simplicity that he can understand the purpose of the treatment and intelligently cooperate with the medical adviser The book, because of the discussion of the methods of treatment, will

be found of great value to the practicing physician who has had less experience in the care of the tuberculous patient. Few authors have made a more frank statement of the value of climate. The six principles laid down rationalize decisions regarding the advisability of seeking climatic change and properly remove from the subject of climate the romantic values that have existed in the optimistic minds of physicians and patients alike.

Of no less value are the equally frank discussions of the employment and continued use of artificial pneumothorax and of the surgical procedures that are now commonly resorted to in treatment. The indications for each method of treatment are outlined, and the advantages of each method are balanced against the disadvantages. Technic is discussed only briefly, Holmes is more interested in the final result.

The book will be of great value to the patient because of the simplicity and clarity of its style. The thoughtful tuberculous person cannot fail to be impressed with the necessity of an exact diagnosis and cannot be ignorant of the facts that must be assembled to make accuracy possible. The patient is made to understand the importance of the presence of a lesion discovered by physical or by roentgenologic examination and the confirmation of its nature by the discovery of *Mycobacterium tuberculosis*. He is led to minimize the relative importance of such common subjective symptoms as fatigue and fever in the absence of objective evidence. After the establishment of an accurate diagnosis, he is informed of the nature of the disease and its symptoms and complications and of his responsibilities both to himself and to those with whom he comes in contact. Moreover, he is left in no doubt about the importance of every method of treatment and of the advantages that are to be expected from each. The book lays down the fundamental principles of the cure of tuberculosis and stimulates the intelligent cooperation of the patient in the treatment advised and employed.

### **The Medicine Man of the American Indian and His Cultural Background**

By William Thomas Corlett, M D, L R C P (Lond), professor emeritus of dermatology-syphilology, Western Reserve University, Fellow of the Royal Society of Medicine of Great Britain, Fellow of the American Medical Association, honorary member and sometime president of the American Dermatological Association, corresponding member of the British Association of Dermatology and Syphilology, Fellow of the American Association for the Advancement of Science. Price, \$5. Pp 327, with 24 illustrations. Springfield, Ill. Charles C Thomas, Publisher, 1935.

This delightful work will entertain and instruct all who may read it. It deals with the origin of the American Indian and his migration from Alaska to the tip of South America. It touches on his culture and the development of his civilization and describes the widely differing degree of cultural advancement among the various tribes.

Into this cultural background steps the "medicine man." He was doctor and priest, soul-saver and body-poisoner, wise counselor and, sometimes, not so wise.

It is generally assumed that the medicine man was somewhat of a charlatan and a quack. Corlett points out that nothing could be further from the truth. There were such persons, just as there are today, but the majority were earnest, studious men whose knowledge and practice might be favorably compared with any in a similar state of scientific advancement. They were carefully chosen, spent much time in study and preparation and devoted their lives to their profession. There were outstanding men among them, just as our own race has its prominent figures. It is pointed out that the practice of medicine among these people was surrounded by greater hazards at that time, not only for the patient but also for the practitioner.

Corlett deals with the different diseases that were encountered in the various localities. He touches on fractures and traumatic surgery among the Indians. There is a discussion of obstetric procedure. The pharmacopoeia of the Indian has been studied. There is further argument about the origin of syphilis.



In concluding his preface the author states "I might add this is not a medical book. It has as much religion as medicine, and more theology than pathology. If it were not so it would not be a true account of the medicine-man of the American Indian." Whether or not it is a medical book, it is most interesting reading for the physician—and for any one else who wishes to indulge a taste for browsing in prehistoric material.

**Chirurgie de l'oesophage** By Raymond Gregoire, professeur a la Faculte de Medecine de Paris, Chirurgien des Hopitaux. Price, 35 francs. Pp 180, with 31 illustrations. Paris: Masson & Cie, 1935.

This monograph on surgery of the esophagus adequately presents the practically important present knowledge concerning the commonly encountered esophageal lesions. Advances in diagnosis and new conceptions of the incidence of certain diseases of the esophagus gained through improved methods of study, such as esophagoscopy, roentgen examination and biopsy, are discussed, and the modern methods of endoscopic and operative treatment are described.

Peptic ulcer of the esophagus is presented as a lesion occurring more frequently than is generally realized. The method of treating this condition is discussed, with special reference to the topical application of silver nitrate solution. In the chapter on esophageal diverticula the methods of diagnosis are well presented. The outline of treatment includes the description and recommendation of a one-stage operation suggested by the author. The theories concerning the etiology of mega-esophagus are presented, and in addition to a consideration of diagnosis, the various methods of dilation and plastic operation applicable in the treatment of this condition are discussed.

The chapter on foreign bodies includes a listing of the indications for approach by esophagoscopy or gastrostomy. Complications, such as perforation, hemorrhage and abscess formation, are described. Gregoire laments the lack of progress in the treatment of cancer of the esophagus. The danger incident to dilation or the implantation of radium in cases of esophageal cancer is shown to detract from the value of these palliative measures. Throughout the book there are pertinent observations on surgical anatomy and pathology. In the last chapter the author outlines the operative approaches and procedures which are available in the surgical treatment of diseases of the esophagus. He is optimistic in regard to the feasibility and good results obtainable through anterior thoracic esophagoplasty.

The book contains thirty-one illustrations, including reproductions of roentgenograms, sketches of operative procedures, photographs of specimens and esophagoscopic images.

**Physical Diagnosis** By Warren P. Elmer and W. D. Rose. Seventh edition. Price, \$5. Pp 919, with 342 illustrations. St. Louis: C. V. Mosby Company, 1935.

The teaching of physical diagnosis has always been a problem. As a separate discipline its origins go back a hundred years to Laennec, Auenbrugger and Skoda. But gradually the technical methods, no longer a novelty, have been more and more absorbed into diagnosis in a broad sense. Most physicians eventually relearn physical diagnosis after years of practice, because the methods work only when used by one sensitive to the problems of disease who more or less knows what he is looking for. The reviewer predicts that as time goes by less and less emphasis will be placed on teaching physical diagnosis as such, this will be learned as an integral part of the general examination and study of patients. Meanwhile it may be said that this book is an excellent exposition of the subject according to present-day standards. As a matter of fact, as its size testifies, it goes somewhat beyond the bounds of the usual compendium of physical diagnosis. The exposition is clear, and the illustrations are excellent.

# Archives of Internal Medicine

VOLUME 57

MARCH 1936

NUMBER 3

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## ACUTE ANTERIOR POLIOMYELITIS

ORTHOPEDIC ASPECTS OF THE CALIFORNIA EPIDEMIC OF 1934

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LOS ANGELES

Anterior poliomyelitis made its appearance in California in 1875, when 2 cases were observed near Eureka. The disease first became epidemic at La Grande, near San Francisco, in 1898. A second epidemic, of relatively few cases, followed in San Francisco in 1902. In 1912 the disease became epidemic in Southern California, 531 cases were reported with 129 deaths. Sporadic cases were reported from time to time until 1925, when the disease again became epidemic, with a total of 821 cases and 144 deaths. Two years later, 1,298 cases were reported, with 224 deaths. During the epidemic of 1930, 1,003 cases were reported, with 157 fatalities.

The outbreak in 1934 showed a decided increase in the number of individual reported cases. This may have been due in part to the increasing alertness of the attending physicians, leading to a recognition of the disease in its preparalytic stage. A total of 3,333 cases, with 110 deaths, were reported by the State Board of Health, the fatality rate being 3.3 per cent.

During the epidemics already mentioned, there has been a steady shift of the incidence to the older age groups. In 1912, only 22 per cent of the patients were over 10 years of age. In 1925, 34.3 per cent were over 10, and in 1930, 40.6 per cent.<sup>1</sup>

From the Department of Orthopedic Surgery, University of Southern California School of Medicine.

Read before the Section on Orthopedic Surgery at the Joint Session of the American Medical Association and the Canadian Medical Association, Atlantic City, N. J., June 12, 1935.

<sup>1</sup> Dunshee, J. D., and Stevens, I. M. Previous History of Poliomyelitis in California, *Am. J. Pub. Health* **24**: 1197 (Dec.) 1934.

In the epidemic of 1934 the incidence according to age was as follows -

Age Group, Years	Cases	Percentage
Under 10	1,389	42.23
10 to 19	993	30.19
20 to 44	847	25.75
45 and older	60	1.83
Total, known ages	3,289	100.00
Age unknown	44	
	3,333	

#### GENERAL OBSERVATIONS

*Geographic Distribution*—The more densely populated centers had the greatest incidence of the disease. Figure 1, a map of the state of California, illustrates this fact. Two thousand, one hundred and twenty cases were reported in Los Angeles County. A large proportion of these cases occurred in the metropolitan area of Los Angeles, the heaviest incidence being in the thickly populated Belvedere residential district, which lies east of the Los Angeles River. In Fresno County, approximately 200 miles north of Los Angeles on the island highway, 204 cases were reported. The city of Fresno is an overnight stopping point in transtate travel. The climate is warm and dry during the summer. The outbreak in the region of San Francisco Bay was next in importance, with 107 cases in Alameda, 123 in San Francisco and 41 in San Mateo counties. In Bakersfield, Orange, San Diego, Tulare, Santa Clara, San Bernardino and Sacramento counties considerable numbers of cases were reported from the more thickly settled sections.

*Seasonal Morbidity*—One hundred cases observed in the orthopedic department of the Los Angeles General Hospital furnish the data for this report. They cannot serve to give a true cross-section of the epidemic because paralysis of a degree is at once presumed on a patient's admission to an orthopedic ward. Many patients were included in the lists of public health reports who presented the picture of a mild and rapidly vanishing illness.

The patients whose cases are included in this report readily group themselves into two classes, adult and juvenile. The affected children exhibited nothing out of the ordinary, while bizarre symptoms and signs characterized the disease in adults.

The epidemic of 1934, as exemplified by this series of cases, reached its height in June (fig. 2). The first patient of this series was seen in January, with an interval until May, when 21 patients were admitted to the hospital. Thirty-five were admitted to the hospital in June, 20 in July, 12 in August, 7 in September, 2 in October and 2 in November.

*Pathology*—In the fatal case in this series autopsy disclosed marked generalized hyperemia of the spinal cord, slight edema and

<sup>2</sup> The statistics were provided by the California State Department of Public Health.



destruction of cells, presumably due to infarction, with normal cells lying adjacent. Extensive cellular infiltration took place in certain cases with disappearance of all nerve elements. An appreciation of the

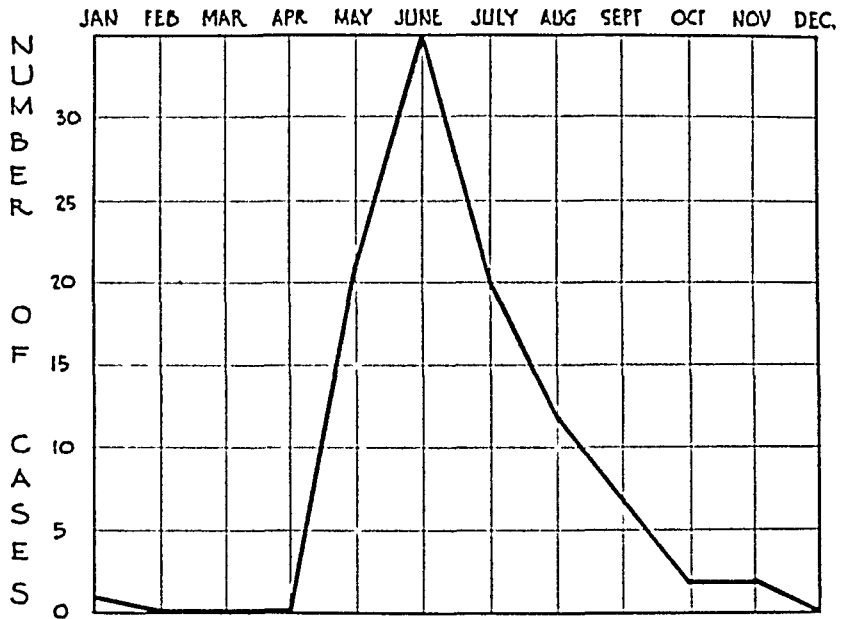


Fig 2—The seasonal morbidity during the epidemic of 1934

TOTAL CASES 100

1<sup>ST</sup> DECADE 35

YOUNGEST 4 MO-  
OLDEST 63 YR

2<sup>ND</sup> DECADE 17

3<sup>RD</sup> DECADE 33

4<sup>TH</sup> DECADE 11

5<sup>TH</sup> DECADE 2

6<sup>TH</sup> DECADE 0

7<sup>TH</sup> DECADE 2

Fig 3—The incidence according to age

pathologic changes serves to formulate an understanding of this disease with special regard to recovery

*Age*—The most striking fact revealed by a study of figure 3 is that 35 of the patients were in the first decade and 33 in the third decade

of life Seventeen were in the second decade, 11 in the fourth, 2 in the fifth and 2 in the seventh

*Sex*—Sixty-four of the patients were females, and 36 were males Four of the males were physicians and at the time of contracting the disease were engaged in the care of patients suffering from acute anterior poliomyelitis Thirty-nine of the female patients were nurses in the Los Angeles General Hospital and for the most part were on duty in the wards for patients with poliomyelitis

#### CLINICAL OBSERVATIONS

*Onset and Complaints on Admission*—This study fails to reveal anything characteristic in the onset of this disease It was abrupt, gradual or insidious One nurse remained on duty at least six weeks after she had contracted the disease and reported her illness only because of increasing muscular weakness

Headache was the most constant symptom, occurring as the only complaint in 49 patients It was frequently (16 patients) associated with backache Aching in the neck was the only complaint of 3 patients, backache of 4, headache, neckache and backache of 3, and backache and neckache of 2

Nausea and vomiting were noted in 44 patients Muscular weakness was a source of alarm to 20 patients, this was not necessarily confined to an extremity or to a single muscle group but was often described as general

Pain in the extremities was not of infrequent occurrence and was noted in the lower extremities 15 times and in the upper extremities 9 times

Nine patients were admitted to the hospital because of acute infections of the upper respiratory tract, with definite characteristics of anterior poliomyelitis developing later

Complaints of limp, muscular twitching, earache, diarrhea, abdominal pain, dysphagia, photophobia, chills, irritability and drowsiness were noted on some occasions

*Findings on Admission*—Rigidity of the neck and back were the most important of the early findings This condition was present in 59 of the patients when they were admitted to the hospital Rigidity of the neck only was noted 3 times and of the back 5 times Muscular weakness and tenderness were detected early in 43 patients Weakness alone was present in 20 and tenderness in 18

Fifteen patients showed a Kernig sign on admission and 16 a Brudzinski sign These signs were present simultaneously in 3 patients The Kernig and Brudzinski signs were demonstrated in 14 patients of 15 years or under and in only 4 patients over 25 years of age

Lethaigy was an occasional finding, being evident in 8 patients. Two patients were dyspneic on admission to the hospital, 4 had muscular twitching and 1, definite dysphagia. Inequality of reflexes was noted in 12 patients, while in 3 the reflexes were hyperactive and in 3 they were not present.

*Spinal Fluid*—Lumbar paracentesis to determine intraspinal pressure and withdrawal of fluid for examination were carried out on 76 patients. Lumbar puncture was not carried out on 24. The spinal fluid of 67 of the 76 patients showed some variation from the normal. The pressure or number of cells was increased, globulin was present or the colloidal benzoin reaction was positive (table 1). All the 9 patients with a

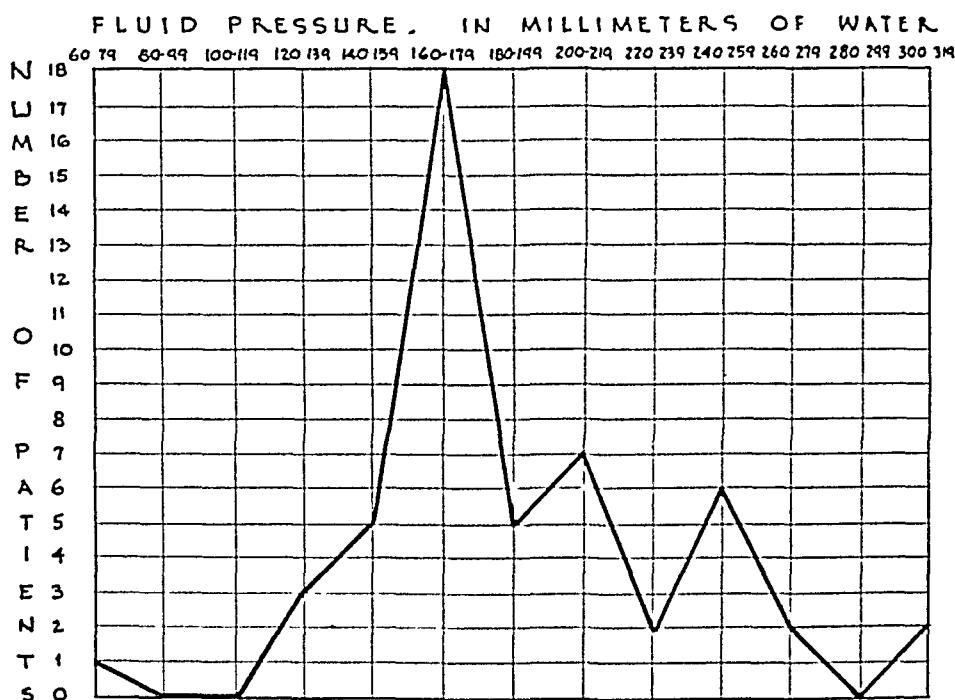


Fig 4—The spinal fluid pressure in millimeters of water

normal spinal fluid had stiffness of the neck and back on admission to the hospital, and subsequently muscular weakness developed.

The spinal fluid pressure varied between 60 and 319 mm of water. Eleven patients had a pressure of 175 mm, 6 of 200 mm and 6 of 160 mm, comprising the largest group (fig 4).

The cellular elements were increased in the spinal fluid of 31 patients. The number of cells per cubic millimeter varied from 12 to 2,200. Lymphocytes predominated in specimens of 27 patients. All the cells were polymorphonuclear leukocytes in 1 specimen. In the remaining 3 specimens there was a high polymorphonuclear cell count (fig 5).

*Character of Muscular Weakness*—Muscular weakness occurred in all 100 patients. The grade of weakness was uniform in some instances,

while in others the degree of paralysis varied with the individual affected muscles. Thirty-six patients suffered a slight degree of muscle weakness, 27 moderate and 23 severe. Severe and moderate paralysis were combined in 9 patients, severe and slight in 3 and moderate and slight in 2.

TABLE 1—*Observations on the Spinal Fluid of 67 Patients\**

Case	Increased Spinal Fluid Pressure	Cells per Cubic Millimeter	Globulin	Colloidal Benzoin Reaction
1	+	0	Trace	Negative
2	+	0	0	0
3	+	0	0	+
4	+	0	0	0
5	0	+	1+	0
6	0	0	0	+
7	0	+	0	0
8	0	0	1+	0
9	+	+	1+	0
10	0	+	Trace	+
11	0	+	1+	+
12	0	+	1+	+
13	0	+	1+	0
14	0	+	1+	+
15	+	+	0	0
16	0	+	Trace	+
17	+	0	0	+
18	+	+	1+	+
19	0	+	0	+
20	+	0	0	0
21	0	0	0	+
22	0	+	2+	+
23	+	0	+	0
24	+	+	0	0
25	+	+	Trace	+
26	+	0	0	0
27	+	+	1+	0
28	+	+	0	+
29	+	0	0	0
30	+	+	0	0
31	+	+	0	0
32	+	+	0	+
33	0	+	1+	0
34	+	0	0	+
35	+	+	0	0
36	+	+	+	+
37	+	+	2+	+
38	+	+	0	+
39	+	0	Trace	0
40	+	+	2+	+
41	+	0	0	0
42	+	+	3+	+
43	0	+	Trace	+
44	+	+	Trace	+
45	+	0	Trace	+
46	+	+	0	+
47	+	+	1+	+
48	+	+	1+	+
49	+	+	2+	+
50	0	0	1+	0
51	+	0	1+	+
52	+	+	2+	+
53	+	0	0	0
54	+	0	Trace	0
55	+	+	1+	+
56	0	+	2+	+
57	+	0	0	0
58	+	0	0	0
59	+	0	Trace	+
60	0	0	Trace	0
61	+	0	0	+
62	+	+	+	+
63	+	+	1+	+
64	+	0	0	+
65	0	0	Trace	+
66	0	0	0	+
67	+	0	0	+

\* There were abnormalities of the spinal fluid of 67 of the 76 patients whose spinal fluid was examined. Examination of the spinal fluid was not carried out on 24 patients.



The distribution of paralysis is indicated in table 2, which is intended to depict the muscular weakness as recorded at the height of the disease

*Condition in Adults*—Perhaps the most interesting clinical features of the epidemic of 1934 are to be found among the adult patients. The

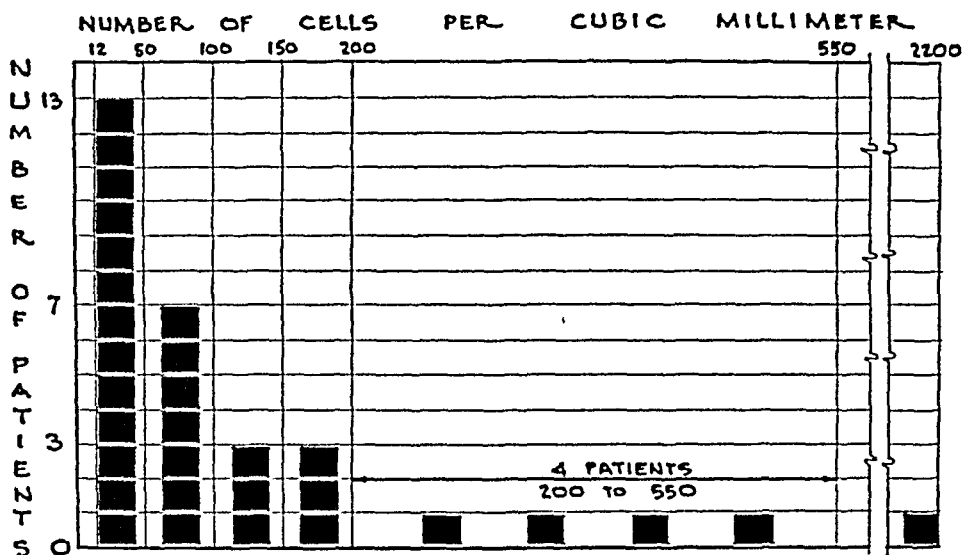


Fig 5—The number of cells per cubic millimeter of spinal fluid

TABLE 2—*Distribution of Paralysis*

Arms		Legs	
Right	2	Right	3
Left	3	Left	8
Right and left +		Right and left	15
Right leg	2		
Left leg	2		
Intercostals	1		
Both legs	10	Right and left --	
Both legs, abdomen	5	Abdomen	7
Left leg, abdomen	2	Diaphragm	1
Both legs, face	1		
Right leg, abdomen	1	Right alone	
Left leg, face	1	Left side of face	1
Right alone +		Abdomen	3
Right leg	3		
Both legs	5	Both legs, both arms and trunk +	
Abdomen	1	Left side of face	1
Right side of face	1	Abdomen	4
Left leg	2		
Left alone +		Gluteal muscles	1
Both legs	9		
Left leg, abdomen	2		
Left leg, left side of face, diaphragm, pharynx	1		

high incidence in the older age groups has already been noted. An unusual contagiousness was apparent in the extraordinary outbreak of the disease among nurses at the Los Angeles General Hospital, where more than 150 nurses were afflicted. Nearly 12 per cent of the hospital employees engaged in caring for the patients in the acute stage contracted the disease, in spite of all the precautionary technic of a well

ordered unit for the care of patients with communicable disease. Clinically the condition in adults was characterized by a predominance of sensory rather than of motor symptoms, by involvement of the joints in a considerable number of cases and by a remarkable tendency to recurrent exacerbation of acute symptoms.

The polyneuritic type of poliomyelitis has long been known as a rare form of the disease<sup>4</sup>. A small sporadic outbreak of a similar condition was described by Kennedy<sup>5</sup> in 1919, under the caption of infective neuronitis, and by Strauss and Rabiner<sup>6</sup> in 1930, who applied the term myeloradiculitis. A certain degree of doubt must be entertained as to the relationship of all these conditions to infantile paralysis of the usual type, since no specific diagnostic test is available.

**Motor Symptoms.** In all adults of this series, numbering 52 patients over 16 years of age, muscular weakness of a greater or less degree was noted. In a number of cases a marked degree of muscular weakness has persisted, without proportionate atrophy and without loss of tendon reflexes or electrical reactions. Involuntary muscular contractions, usually painful, were a troublesome complaint in certain cases. These consisted of twitching, clonic movements and cramps in the affected muscles. Muscular incoordination was occasionally a striking feature. In 1 case incoordination of the intercostal muscles and the diaphragm necessitated a short period of treatment in the respirator. Long after normal contractile power returned, the patients complained of persistent fatigue and lack of endurance.

**Sensory Symptoms.** Sensory rather than motor symptoms, however, dominated the picture in most of the adult patients. The outstanding complaint was pain in the back and in the extremities. In the cases of milder involvement this appeared not unlike the muscular tenderness commonly seen in typical poliomyelitis but more intense, more prolonged and likely to recur at intervals. In the cases of severe involvement the pain was intractable, excruciating and persistent for weeks or even months. Only partial relief could be obtained, even with large doses of opiates.

Invariably associated with the pain was local tenderness of the muscles, sometimes generalized but often confined to certain groups. In a number of cases the tenderness was most pronounced at the musculo-tendinous junctions. In a few cases there was definite tenderness of the nerve trunk.

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4 Wickman, Otto Ivar. *Acute Poliomyelitis, Nervous and Mental Disease Monograph 16*, New York, Nervous and Mental Disease Publishing Company, 1913.

5 Kennedy, Foster. *Infective Neuronitis*, *Arch Neurol & Psychiat* **2** 621 (Dec) 1919.

6 Strauss, Israel, and Rabiner, Abraham. *Myeloradiculitis. A Clinical Syndrome*, *Arch Neurol & Psychiat* **23** 240 (Feb) 1930.

Hyperesthesia, paresthesia and areas of anesthesia were also encountered, sometimes following the distribution of the nerve trunks and sometimes involving an entire extremity

**Vasomotor and Trophic Changes** Vasomotor and trophic disturbances were almost constant findings among the adult patients. Excessive sweating or abnormal dryness of the skin of the extremities, together with coldness and cyanosis, were the phenomena usually observed. In the cases of more severe involvement exfoliation of the skin of the affected extremities occurred, followed by glossy atrophy of the skin and atrophy of the subcutaneous tissue. Hypertrichosis and brittleness of the nails, with retardation or acceleration of growth, were often noted. It was the impression of many observers that a generalized disturbance of vasomotor control occurred in these patients, which best explained the emotional instability (occurring in 30 per cent of the cases) and the exacerbations of acute symptoms, to be described later.

TABLE 3—*Distribution of Involvement in the Joints in the Adult Patients*

Joints	No. of Cases
Fingers and wrists	3
Shoulder, elbow, wrist and fingers	3
Shoulder, elbow and knee	1
Shoulder alone	1
Hip and knee	1
Both knees	1
Both knees and ankles	1
Multiple arthritis in all four extremities	1

**Arthritis** A unique feature of this epidemic was the occurrence of inflammatory changes in and about the joints, which was observed in 34 per cent of the adult patients in the present series. In 10 per cent there were merely transitory but sharply localized pain and tenderness in the joints. Definite proliferative changes about the joints occurred, however, in the remaining 24 per cent. In the earlier stages of the disease, swelling and intense pain were present, sometimes with increased synovial fluid. Later, the acute inflammation was followed by fibrosis and contracture of the joint capsules, resulting in limited motion. Trophic changes, as described earlier, were usually present. In all these cases muscular weakness occurred in the affected extremities.

The distribution of involvement of the joints in the more severe cases is set forth in table 3.

**Exacerbations** The clinical course of the adult patient was marked in 52 per cent of the cases by a tendency to recurrent attacks of acute symptoms, usually consisting of pain in the back and extremities, headache, photophobia and severe vomiting. Increased intrathecal pressure was of course suspected and was sometimes found, but in many instances the spinal fluid pressure was not increased. These exacerbations of the

acute symptoms often occurred after the patient had apparently recovered and had returned to work. Although they sometimes occurred spontaneously, the attacks were more commonly precipitated by emotional strain or fatigue. In some cases they resulted from a too early attempt to institute physical therapy. In other cases they were apparently related to changes in the weather or to the onset of menstruation. The duration of these attacks varied from a day or two to several weeks, and the severity also varied from that of a mild indisposition to a prostrating illness, in which prolonged vomiting necessitated parenteral administration of fluids and dextrose for days at a time.

#### COMPLICATIONS

Among the children of this series the following complications occurred. One child survived an attack of pneumonia. In 1 secondary anemia developed. Two required treatment in the respirator. Mild scoliosis developed in 4. One suffered from an attack of osteomyelitis of the femur coincident with the onset of poliomyelitis.

The adults suffered from a somewhat different group of complications. Scoliosis has not been observed thus far. Disturbances of the menstrual cycle have been almost constant among the women. Other complications have occurred as follows:

	Cases
Thrombophlebitis of leg	2
Pneumonia	2
Cystitis	3
Renal calculus	2
Urinary incontinence	1

#### TREATMENT

All patients with acute poliomyelitis were hospitalized under quarantine in the Communicable Disease Unit of the Los Angeles General Hospital as soon as the diagnosis was established, and they were treated with absolute rest and early splinting of the affected regions, an orthopedic consultant being in attendance from the day the patient was admitted. Bradford frames were used, with attached and adjustable abduction arm splints and posterior wire leg splints.

In all cases in which the condition was recognized during the acute stage of the disease, convalescent serum, alternated with pooled adult serum, was administered intramuscularly and intravenously in amounts varying from 30 to 175 cc. The end-results in relation to serum therapy are indicated in table 4. Of the 14 patients with a severe degree of residual paralysis, all but 1 received serum. There was a definitely higher incidence of motor recovery, however, in the group that was treated with serum.

Immediately on release from quarantine, all patients showing a marked degree of paralysis were transferred to the orthopedic wards. Those with a milder degree of paralysis were cared for in convalescent wards and were discharged to the outpatient department.

Physical therapy was begun, whenever possible, as soon as the patient was released from quarantine. Warm salt baths were usually the first measure employed, followed by systematic muscle training as soon as muscular tenderness subsided. Among the children, this was nearly always possible in the fourth or fifth week. The adults, on the other hand, provided an entirely different problem. Except in those whose course followed that of the juvenile type of the disease, it was noted that

TABLE 4—*End-Results in Relation to Serum Therapy*

	Received Serum (78)		No Serum (22)	
	Number	Per Cent	Number	Per Cent
Motor recovery	54	69.0	10	45
Persistent paralysis, mild	10	13.0	11	50
severe	13	16.7	1	5
Died	1	1.3	0	0

TABLE 5—*Present Status of the One Hundred Patients*

	Children (48)		Adults (52)		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Complete recovery	21	44	24	46	45	45
Complete motor recovery but still disabled	0	0	19	37	19	19
Muscular weakness still present	27	56	8	15	35	35
Slight degree	16	33	5	10	21	21
Severe degree	11	23	3	5	14	14
Died	0	0	1	2	1	1

persistent pain and tenderness prevented any active physical therapy in the early weeks of the illness. Attempts to begin even the gentlest treatment, such as immersion for a few minutes in a warm salt bath, often precipitated a violent exacerbation of symptoms, and it soon became evident that the only measures that could be safely applied at this stage were gentle massage and assisted active movements for the affected joints. These measures were carried out in the ward, without removing the patient from the bed. Eventually, after many weeks, the patients became able to tolerate underwater therapy, which has been of great assistance in restoring function.

The sensory symptoms in adults have been peculiarly resistant to medication. The most effective measures have been absolute rest, including immobilization of all four extremities, good nursing care and

parenteral administration of fluid and dextrose in cases of excessive vomiting

Spinal puncture relieved severe headache in some cases, and it was felt that retention enemas of a hypertonic solution of magnesium sulfate or sodium chloride were also of some value during acute exacerbations, but the reaction to these procedures was not constant

#### PRESENT STATUS

The progress of the 100 patients up to May 15, 1935, is set forth in table 5. Fourteen of the group were still severely paralyzed, and recovery seemed doubtful. The remainder were expected eventually to make a good functional recovery.

In the group of 19 adults who were still disabled, although fully recovered from all objective evidence of muscular weakness, the following symptoms and findings are held responsible for disability:

	Cases
Headache	8
Pain in one or more limbs	8
Fatigue	7
Arthritis	7
Emotional instability	3
Renal calculus	2

#### COMMENT

The striking difference between the condition in the children and that in the adults in this series arouses at once a doubt as to the correctness of the diagnosis. Were we dealing with two different diseases, or did the same virus produce a different clinical picture in adult patients?

In support of the contention that the condition in adults was an atypical form of true anterior poliomyelitis, the following considerations are submitted:

1 The cases occurred at the height of an epidemic in which a majority of cases were instances of typical poliomyelitis affecting children.

2 Most of the adult patients in this series were nurses engaged in caring for patients with poliomyelitis in the acute stage.

3 Muscular weakness was noted by competent observers in every case, and in 35 cases, paralysis has persisted up to the time of writing.

The criticism has also been made that many of the late symptoms complained of by the adult patients may have been of functional origin. The cases of milder involvement with many subjective complaints, if encountered individually might well give this impression. The striking uniformity of the clinical picture presented by the patients,

however, and the prostrating severity of the symptoms in many cases led most observers to believe that an organic basis for the complaints was present in virtually every case

#### SUMMARY

The 1934 epidemic of poliomyelitis was more extensive than any previous outbreak in California and was relatively mild, the fatality rate being 33 per cent

Peculiar features of this epidemic were the unusual communicability of the disease, the early peak (in June) and the large number of adults affected

In children, the disease followed the usual clinical course

Among the adults, an atypical form of the disease was observed, in which sensory, vasomotor and arthritic symptoms predominated and recurrent exacerbations of acute symptoms occurred

#### ABSTRACT OF DISCUSSION

DR WILLIAM H PARK, New York The epidemic of poliomyelitis in Los Angeles was most interesting from the medical standpoint It is doubtful whether all the suspected cases were instances of poliomyelitis

During the last few years most people lost faith in the use of antipoliomyelitis serum in the treatment of poliomyelitis in the preparalytic stage This is largely due to the fact that in several outbreaks only a portion of the children were given the serum, while the others were used as controls Dr Kramer and Dr Aycock started a parallel series of tests in two hospitals, in which only one half of the patients were treated with antiserum At the end of the epidemic there were no apparent differences between the results in the untreated and those in the treated patients In New York, where nearly 1,000 patients in the preparalytic stage were divided so that about one half were untreated and a little more than half were treated, no differences were noted It will be noted that where control cases have been used serum is usually no longer employed Where control cases have not been used, physicians are giving the serum

Dr Brebner had an opportunity in 1931 to administer the antiviral serum as a preventive measure It seemed to be of value, but more cases must be observed before one can be sure Of the group treated, poliomyelitis developed in only 1 and was very mild, while of twice the number of untreated children poliomyelitis developed in 13 or 14 after 1,200 were immunized

There are two vaccines, of one Dr Kolmer will speak, the other was developed by Dr Brodie Dr Kolmer's is virulent for monkeys but apparently not for human beings According to Dr Brodie's method, the vaccine is treated with a solution of formaldehyde, left for from six to eight hours in the icebox and then used It is known that two injections of vaccine will produce a definite humoral immunity in infants or children If there is the slightest immunity already present, even one injection will establish it As those who have no immunity are those most liable to the disease, I think that two injections should be given

During this winter in Kern County, Calif, there was a small epidemic About 70 cases of poliomyelitis were reported The vaccine was given to about

1,500 young persons. Poliomyelitis did not develop in any of the treated children. There is a possibility, therefore, that the vaccine did good. It will be interesting to administer the vaccine on a larger scale this summer. I hope to give it free of charge in certain states where it is needed.

DR PHILIP LEWIN, Chicago. Up to the time that I read Dr. Wilson's paper my impression had been that the usual number of cases of poliomyelitis occurred in Los Angeles and that coincidentally another disease became epidemic.

The significant features which were in contrast to poliomyelitis, as I understand it, were the following: (1) too early occurrence of the peak of the epidemic, i. e., in May and June, (2) the high incidence of communicability, (3) the high incidence in adults—4 physicians and 39 nurses, (4) the atypical course in adults, (5) the mildness of the attack, (6) the marked degree of muscle weakness without proportionate atrophy and without loss of tendon reflexes or electrical reactions, and (7) the recurrences.

There is probably a high incidence of infection in cases of poliomyelitis but a low incidence of contagion-producing paralysis. One may have a subclinical form without cerebrospinal infection.

Examination must be made deliberately. A proper examination during the systemic or preparalytic stage requires about one hour. It is practically impossible for health officers, under the present regimen and especially during an epidemic, to spend that much time.

One of the important findings was "spotty motor paralysis" without sensory paralysis. Two of the most important reflexes during the early stage are the abdominal and the cremasteric reflex. If a physician sees a patient in the morning with active or hyperactive knee jerks and the knee jerks cannot be elicited at the end of that day or the next, this is in favor of a diagnosis of infantile paralysis.

During the systemic phase and the preparalytic stage, the differential diagnosis must include epidemic meningitis and tuberculous meningitis. Encephalitis must be distinguished from an early stage of bulbar poliomyelitis. Acute rheumatic fever and articular rheumatism must be differentiated. Polyneuritis is associated with sensory disturbances. Osteomyelitis and scurvy each have their characteristic symptoms. Central pneumonia with toxic encephalitis may present some difficulty in diagnosis. Diphtheritic neuritis may have to be differentiated.

One of Dr. Legg's patients, who had 600 cells per cubic millimeter of spinal fluid, proved to have mumps.

In children and adults one should inject intraspinally 5 cc less of convalescent serum than the amount of fluid removed, which is usually 25 cc, and intravenously 60 cc. In adults one should inject about 20 cc intraspinally and 160 cc intravenously. Serum should not be given intraspinally in cases of bulbar poliomyelitis or to patients with a normal spinal fluid cell count. From 1916 to 1931 the reports on serum therapy were favorable. But since the report of Park, the reverse has been true. It may well be that the preparation, dosage and administration are inadequate. In the absence of a proved specific and in the absence of proof of its ineffectiveness, I shall continue to recommend the use of convalescent serum during the preparalytic stage. One cannot look for significant progress in the treatment of poliomyelitis except from biologic sources, such as vaccines and serums.

The operations for the residual effects of poliomyelitis are well standardized. New procedures will be designed for special conditions, but the most important attack of the future will probably be from the biologic standpoint.



It is hoped that by the use of protective vaccines, early diagnosis and the prompt administration of convalescent serum paralysis can be eliminated in the disease called anterior poliomyelitis

DR JAMES P LEAKE, Washington, D C I agree with Dr Wilson's conclusions that the matter of the exact identity of the condition in some of these cases in adults should be left open at present His analysis from the point of view of an orthopedic surgeon, however, leaves the impression that the condition was probably atypical poliomyelitis, in spite of some evidence to the contrary I want to say merely that the condition as I observed it in Los Angeles was not at all encephalitic, and I do not think that it corresponded to the Australian X disease

DR MAURICE BRODIE, New York I just mentioned to Dr Leake that I thought this disease resembled the Australian X disease I thought that there was evidence of involvement of the upper motor neurons that accounted for some of the unusual symptoms in the cases of poliomyelitis in adults For example, there was a certain amount of emotional upset, and the paralysis seemed to resemble involvement of the upper motor neurons, with no atrophy to speak of However, the authors did not mention whether there was any spasticity The Australian X disease likewise included involvement of the upper motor neurons and perhaps involvement of the autonomic nervous system, and it is known that in some of the cases the disease was poliomyelitis, for Breinl transmitted the disease to monkeys, although others had shown by experiments in sheep that the disease in some patients was encephalitis Poliomyelitis as it is usually known involves the cord and some of the brain stem, but in the cases in California it may have involved the higher centers The sensory manifestations were not altogether out of gear They have been reported, and in my experimental study of monkeys I have noted involvement of the posterior ganglions Some of the neurons of the lumbar and cervical ganglions showed nearly all the cells to be destroyed

Dr Lewin showed a chart of systemic reactions and indicated that the virus travels from the nose to the blood and thence to the central nervous system However, the virus most likely travels along nerve paths, and so virus is fixed in the nervous system To give serum at any stage would be analogous to treating diphtheria four or five days after infection is established, when the toxin is fixed to the tissues and cannot be dislodged with an antibody

# UNCOMPLICATED AURICULAR FIBRILLATION AND AURICULAR FLUTTER

FREQUENT OCCURRENCE AND GOOD PROGNOSIS IN PATIENTS  
WITHOUT OTHER EVIDENCE OF CARDIAC DISEASE

EDWARD S ORGAIN, M D

LOUIS WOLFF, M D

AND

PAUL D WHITE, M D

BOSTON

Auricular fibrillation and auricular flutter are common and well recognized disorders of cardiac rhythm. Less well appreciated, however, is their occurrence in persons without other signs of cardiac disease. To emphasize the frequency of this occurrence and to demonstrate its good prognosis constitute the main objects of the present communication.

## REVIEW OF THE LITERATURE

Premature beats<sup>1</sup> and paroxysmal tachycardia<sup>2</sup> have long been known to occur in healthy persons. That auricular fibrillation may arise in a heart previously healthy was first pointed out by Gossage and Hicks<sup>3</sup> in 1913, although Fox<sup>4</sup> and Mackenzie<sup>5</sup> a few years before noted no evidence of cardiac disease in several of their cases. Since these early communications there have appeared in the literature numerous reports of auricular fibrillation occurring in persons with a clinically normal heart as a result of varied stimuli—toxic, traumatic and reflex—and without any obvious cause. The following list has been

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From the cardiographic laboratory and cardiac clinics of the Massachusetts General Hospital

1 Mackenzie, J. Diseases of the Heart, ed 3, New York, Oxford University Press, 1913

2 Bristowe, J. S. On Recurrent Palpitations of Extreme Rapidity in Persons Otherwise Apparently Healthy, *Brain* **10**:164, 1888

3 Gossage, A. M., and Hicks, J. A. B. On Auricular Fibrillation, *Quart J Med* **6** 435, 1913

4 Fox, G. H. The Clinical Significance of Transitory Delirium Cordis, *Am J M Sc* **140** 815, 1910

5 Mackenzie, J. *Brit Med J*, **1** 273, 1910-1911

assembled to show many interesting examples noted in the literature and in our own cases

# 1 Toxic factors

## A Infections

- Pneumonia <sup>6</sup>
- Influenza <sup>7</sup>
- Osteomyelitis <sup>6b</sup>
- Gastro-enteritis <sup>6b</sup>
- Malarial chill <sup>8</sup>
- Pelvic abscess <sup>8</sup>

## B Drugs

- Epinephrine <sup>9</sup>
- Digitalis <sup>10</sup>
- Acetylsalicylic acid <sup>11</sup>
- Ether <sup>12</sup>

## C Other chemical agents

- Alcohol <sup>11</sup>
- Tobacco <sup>11</sup>
- Hydrogen sulphide <sup>15</sup>
- Arsenic <sup>16</sup>
- Gas (CO) in a refrigerator car <sup>12b</sup>
- Gasoline fumes (?) <sup>12b</sup>

## D Diabetic coma <sup>17</sup>

6 (a) Krumbhaar, E B Transient Auricular Fibrillation, Arch Int Med **18** 263 (Aug) 1916 (b) Parkinson, J, and Campbell, M Paroxysmal Auricular Fibrillation A Record of Two Hundred Patients, Quart J Med **23** 67, 1930 (c) Cases in this series

7 Patterson R V Transient and Recurrent Auricular Fibrillation, J A M A **82** 453 (Feb 9) 1924

8 Instances of auricular fibrillation of this type occurred in our series

9 Hume, W E The Action of Adrenaline Chloride on the Human Heart, Quart J Med **21** 459, 1927 Smith, F M, and Moody, W B The Induction of Premature Contractions and Auricular Fibrillation by Forced Breathing, Arch Int Med **32** 192 (July) 1923

10 Brams and Gaberman, quoted by McEachern and Baker <sup>20f</sup>

11 Dutt Gupta, A K A Case of Auricular Fibrillation After Aspirin, Indian M Gaz **63** 531, 1928

12 (a) Levine, S A Acute Cardiac Upsets Occurring During or Following Surgical Operation, J A M A **75** 795 (Sept 18) 1920 (b) Fowler, W M, and Baldrige, C W Auricular Fibrillation as the Only Manifestation of Heart Disease, Am Heart J **6** 183, 1930 (c) Fox <sup>1</sup>

13 (a) Wolferth, C C Intermittent Auricular Fibrillation, Arch Int Med **36** 735 (Nov) 1925 (b) Fowler and Baldrige <sup>12b</sup> Patterson <sup>7</sup> Cases also occurred in our series

14 Laslett, E E Notes on Four Cases of Paroxysmal Tachycardia, Quart J Med **15** 18, 1921

15 Robinson, G C Transient Auricular Fibrillation in a Healthy Man Following Hydrogen Sulphide Poisoning, J A M A **66** 1611 (May 20) 1916

16 Cassidy, M, quoted by Cowan <sup>21</sup>

17 Borg, J F Diabetic Acidosis Etiological Factor in Production of Auricular Fibrillation, Minnesota Med **11** 580, 1928

- 2 Trauma
  - A Injuries
    - 1 To the head <sup>18a</sup>
    - 2 To the chest <sup>18b</sup>
  - B Shock
    - Electric <sup>19</sup>
  - C Instrumentation to the ear <sup>12b</sup>
  - D Burns <sup>8</sup>
- 3 Reflex
  - A Appendicitis <sup>19a</sup>
  - B Gallbladder colic <sup>20</sup>
  - C Peptic ulcer <sup>20a</sup>
  - D Indigestion and overeating <sup>21</sup>
  - E Cough <sup>3</sup>
  - F Vomiting <sup>8</sup>
  - G Operation <sup>8</sup>
- 4 Exertion <sup>22</sup>
- 5 Nervous disturbance
  - A Excitement <sup>23</sup>
  - B Emotion <sup>24</sup>
- 6 Miscellaneous
  - Kyphoscoliosis <sup>25</sup>
- 7 No apparent cause <sup>26</sup>

18 (a) Bramwell C Can a Head Injury Cause Auricular Fibrillation? *Lancet* **1** 8, 1934 (b) Kahn, M H, and Kahn, S Cardiovascular Lesions Following Injury to the Chest, *Ann Int Med* **2** 1013, 1929

19 (a) Jaksch-Warthenhorst, R, and Rihl, J Vorhofsfimmern nach elektrischem Trauma, *Ztschr f d ges exper Med* **50** 110, 1926 (b) Hay, J, and Jones, H W Trauma as a Cause of Auricular Fibrillation, *Brit M J* **1** 559, 1927 (c) Laslett, E E A Paroxysm of Auricular Fibrillation Caused by Electric Shock, *ibid* **1** 919, 1927

20 (a) Felderbaum, D, and Finesilver, B Transient Auricular Fibrillation in Abdominal Diseases, *Am Heart J* **2** 416, 1927 (b) Footnote 8

21 Cowan, J The Causes of Auricular Fibrillation, *Quart J Med* **22** 237, 1929

22 Reid, W D Auricular Fibrillation in an Apparently Normal Heart, *Boston M & S J* **197** 1213, 1927 Fowler and Baldrige <sup>12b</sup> Hay and Jones <sup>19b</sup> Wolferth <sup>13a</sup> Laslett <sup>14</sup> Cases also occurred in our series

23 Semerau, M Ueber Ruckbildung der Arrhythmia perpetua, *Deutsches Arch f klin Med* **126** 161, 1918 Fowler and Baldrige <sup>12b</sup> Hay and Jones <sup>19b</sup> Laslett <sup>14</sup> Footnote 8

24 Heitz, J La forme paroxystique de l'arythmie complete, *Ann med* **1** 483, 1914 Mouquin, M Les formes paroxystiques de l'arythmie complete, *Medecine* **8** 420, 1927 Footnote 8

25 Boas, E P The Cardiovascular Complications of Kyphoscoliosis with Report of a Case of Paroxysmal Auricular Fibrillation in a Patient with Severe Scoliosis, *Am J M Sc* **166** 89, 1923

26 Levine, S A Auricular Fibrillation Some Clinical Considerations, *Am J M Sc* **154** 43, 1917 Smith, F J, and Clark, N E Quinidine in the Treatment of Auricular Fibrillation—Established, Paroxysmal, and Transient, *Arch Int Med* **36** 839 (Dec) 1925 Parkinson and Campbell <sup>6b</sup>

Fowler and Baldrige,<sup>12b</sup> reemphasizing the association of varied stimuli, collected the reports of 35 such cases from the literature, to which they added 10 of their own. The most comprehensive review of the subject of paroxysmal auricular fibrillation has been contributed by Parkinson and Campbell<sup>6b</sup> in their report of 200 cases, in 15 per cent (30 cases) of which there was no evidence of cardiac disease. Recently, Weisman<sup>27</sup> and Gold, Otto and Satchwell<sup>28</sup> have mentioned several cases without giving any details, and Bramwell<sup>18</sup> has recorded the case of a healthy man in whom fibrillation followed trauma to the head. Discussions on the possible etiologic factors and mechanisms involved in the genesis of fibrillation have been presented by many authors<sup>29</sup> and need not be reviewed here. Among others, Yater,<sup>30</sup> and Mohler and Crawford<sup>31</sup> have clearly demonstrated that there is no pathologic change in the heart characteristic of auricular fibrillation.

The view that auricular flutter may occur with no other sign of cardiac disease was first advanced by Ritchie<sup>32</sup> in 1914, but Lewis,<sup>33</sup> Mackenzie<sup>1</sup> and Cowan<sup>34</sup> had previously reported cases in which no evidence of cardiac disease was shown. Similarly, a case of Parkinson and

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27 Weisman, S. A. Auricular Fibrillation. Ambulatory Treatment with Quinidine, *Arch Int Med* **49** 728 (May) 1932.

28 Gold, H., Otto, H. L., and Satchwell, H. The Use of Quinidine in Ambulatory Patients for the Prevention of Paroxysms of Auricular Fibrillation and Auricular Flutter, *Am Heart J* **9** 219, 1933.

29 (a) Robinson, G. C. Paroxysmal Auricular Fibrillation, *Arch Int Med* **13** 298 (Feb.) 1914. (b) Lewis, T. The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, Shaw & Sons, Ltd., 1925, p. 387. (c) Carter, E. P., Andrus, E. C., and Dieuaide, F. R. A Consideration of the Cardiac Arrhythmias on the Basis of Local Circulatory Changes, *Arch Int Med* **34** 669 (Nov.) 1924. (d) de Boer, S. Nature et origine de la fibrillation, *Arch mal du cœur* **20**:137, 1927. (e) Andrus, E. C., and Carter, E. P. The Refractory Period of the Normally Beating Dog's Auricle with a Note on the Occurrence of Auricular Fibrillation Following a Single Stimulus, *J Exper Med* **51** 357, 1930. (f) McEachern, D., and Baker, B. M. Auricular Fibrillation. Etiology, Age, Incidence, and Production by Digitalis Therapy, *Am J M Sc* **183** 35, 1932.

30 Yater, W. M. Pathologic Changes in Auricular Fibrillation and in Allied Arrhythmias, *Arch Int Med* **43** 808 (June) 1929. Gossage and Hicks.<sup>3</sup> Fowler and Baldrige.<sup>12b</sup> Bramwell.<sup>18</sup> Patterson.<sup>7</sup> Felberbaum and Finesilver.<sup>20a</sup> Cowan.<sup>21</sup>

31 Mohler, H. K., and Crawford, B. L. Pathological Changes in the Heart in Auricular Fibrillation, *Am J M Sc* **187** 171, 1934.

32 Ritchie, W. T. Auricular Flutter, London, E. W. Green & Son, Ltd., 1914.

33 Lewis, T. Observations on a Curious and Not Uncommon Form of Extreme Acceleration of the Auricle. Auricular Flutter, *Heart* **4** 171, 1912-1913.

34 Cowan, J. Diseases of the Heart, Philadelphia, Lea & Febiger, 1914, p. 207.

Mathias<sup>35</sup> and several instances by Blackford and Willius<sup>36</sup> were recorded in which toxic or infectious factors were presumably responsible for flutter in hearts probably otherwise normal. Single instances without an obvious cause, though in several the paroxysms were precipitated by exertion, have been presented by Keating and Hajek,<sup>37</sup> Scott,<sup>38</sup> Gallavardin, Bonnamour and Bernheim,<sup>39</sup> Sprague and White<sup>40</sup> and Bourne<sup>41</sup>. Two patients were observed by Mackenzie<sup>42</sup> (one previously reported by Lewis) over forty years after what was probably the first appearance of paroxysms of auricular flutter. Parkinson and Bedford<sup>43</sup> in their review of fifty-two cases of flutter found no evident cardiac disease in five patients followed for many years and concluded that "occasionally like paroxysmal tachycardia and extrasystoles, flutter is the only evidence of cardiac abnormality—no more than a functional disturbance."

Nervous influences, sympathetic (accelerator) stimulation, combined with lack of vagal inhibition, either alone<sup>32</sup> or with an accompanying pathologic change in the auricular musculature,<sup>37</sup> have been proposed to explain the production of flutter in these patients.

From a consideration of the literature it is thus obvious that the concept of severe disturbances of cardiac rhythm occurring in the absence of other manifestations of cardiac disease is not new. Wilson, Wishart, MacLeod and Barker<sup>44</sup> have reported that even ventricular tachycardia, an arrhythmia usually dependent on serious cardiac pathologic change, may be present with no other sign of cardiac disease.

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35 Parkinson, J, and Mathias, H H. Tachycardia of Auricular Origin and Flutter with Phasic Variation in Auricular Rate and in Conduction, *Heart* **6** 27, 1915

36 Blackford, J M, and Willius, F A. Auricular Flutter, *Arch Int Med* **21** 147 (Jan) 1918

37 Keating, J H, and Hajek, J. Auricular Flutter with Report of Cases, *Am J M Sc* **164** 656, 1922

38 Scott, R W. A Case of Auricular Flutter with Paroxysmal Attacks of 1:1 Conduction, *J A M A* **79** 1984 (Dec) 1922

39 Gallavardin, L, Bonnamour, S, and Bernheim, M. Un cas de flutter 1:1, *Arch d mal du cœur* **17** 342, 1924

40 Sprague, H B, and White, P D. Auricular Flutter. Report of a Case of Five Years' Duration with Spontaneous Restoration to Normal Rhythm, *J A M A* **90** 1772 (June 2) 1928

41 Bourne, G. Three Cases of Paroxysmal Auricular Flutter, *Lancet* **1** 686, 1933

42 Mackenzie, J. *Diseases of the Heart*, ed 4, New York, Oxford University Press, 1925

43 Parkinson, J, and Bedford, D E. The Course and Treatment of Auricular Flutter, *Quart J Med* **21** 21, 1927

44 Wilson, F N, Wishart, S W, MacLeod, A G, and Barker, P S. A Clinical Type of Paroxysmal Tachycardia of Ventricular Origin in Which Paroxysms Are Induced by Exertion, *Am Heart J* **8** 155, 1933

Levine and Sturgis<sup>45</sup> have long emphasized the importance of auricular fibrillation, particularly in its transient form, as a sign of unrecognized hyperthyroidism. Similarly, Wohl<sup>46</sup> has mentioned hyperthyroidism masked as auricular flutter.

During the past twenty years few significant follow-up studies<sup>47</sup> have appeared demonstrating the actual prognosis in these cases of auricular fibrillation or of auricular flutter. We have observed a large group of patients, and have deemed it worth while to report on the cases after a sufficient number of years had elapsed to make the study of value.

### MATERIAL AND OBSERVATIONS

This report comprises observations on 49 cases of auricular fibrillation and 7 cases of auricular flutter in none of which definite evidence of cardiac disease was demonstrated by history, physical examination, roentgen study or electrocardiograms of the patients. Two cases are included in both groups<sup>48</sup> because the patients presented at different times paroxysms of both disorders. Automatically excluded were those cases in which the patient offered any sign of the common factors usually held responsible for these forms of arrhythmia, namely, rheumatic fever, disease of the coronary arteries, hypertension and hyperthyroidism. No case was rejected because of age or the presence of peripheral arteriosclerosis.

The majority of cases were derived from private practice, and an idea of the incidence of such cases can be gained from the following data. Of 5,000 patients seen in consultation for some complaint relative to the heart, 583 (11.6 per cent) had auricular fibrillation and 38 (0.76 per cent) auricular flutter. In 36 (6.2 per cent) of the former and 5 (13.2 per cent) of the latter these disorders were not accompanied by detectable cardiac disease.

For reasons of simplicity and clarity it seems best that we present the observations on the two groups of auricular fibrillation and auricular flutter separately.

### AURICULAR FIBRILLATION

In the group of 49 cases of auricular fibrillation the diagnosis was made by electrocardiograph in 25, through observation of an attack by a physician in 21 and on the basis of a typical history of paroxysmal attacks of irregular prolonged palpitation with sudden onset and offset in the remaining 3.<sup>49</sup>

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45 Levine, S. A., and Sturgis, C. C. Hyperthyroidism Masked as Heart Disease, *Boston M. & S. J.* **190** 233, 1924. Levine, S. A. Unrecognized Hyperthyroidism Masked as Heart Disease, *Ann. Int. Med.* **4** 67, 1930.

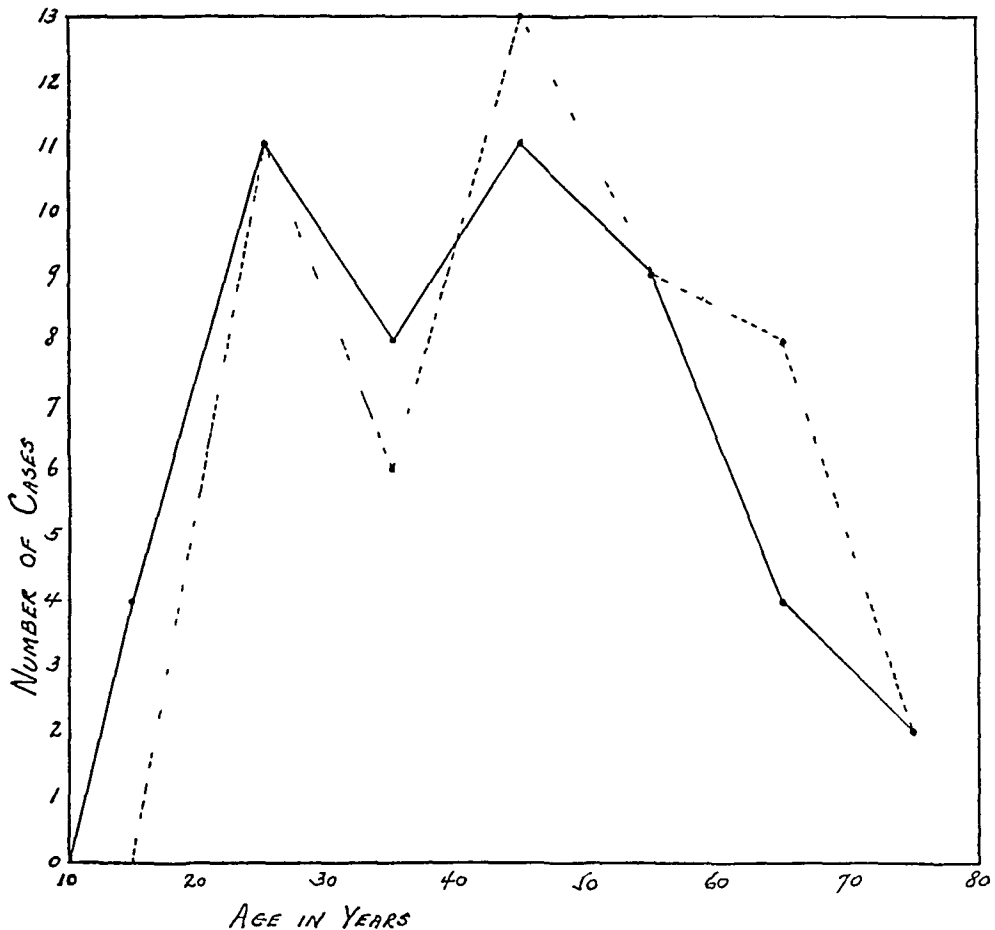
46 Wohl, M. G. Hyperthyroidism Masked as Hypertension. *Auricular Flutter*, *M. Clin. North America* **17** 751, 1933.

47 Mackenzie<sup>1</sup> Parkinson and Campbell<sup>4b</sup> Mackenzie<sup>12</sup> Parkinson and Bedford<sup>43</sup>

48 Cases 23 and 24 of auricular fibrillation correspond to cases 6 and 4 of auricular flutter.

49 Case 12 has been previously reported by Wolff, Parkinson and White (*Am. Heart J.* **5** 685, 1930). The patients in cases 1, 2 and 14 are brothers and will be reported on in detail by one of us (L. W.).

The ages varied from 21 to 75 years, and when classified according to age at onset 23 patients were under 40. Forty-four were men and 5 were women. Eighty per cent of the men were engaged in occupations requiring mental as opposed to physical effort, 30 per cent were physicians. The women were chiefly housewives. The most frequent symptom of paroxysmal fibrillation was irregular, rapid palpitation, abrupt in onset, variable in duration and sudden in termination. Less commonly encountered were weakness, dizziness, faintness, nervousness and pain, precordial or substernal. In its established form fibrillation was usually present without palpitation save on effort. No patient showed any evidence of



Distribution according to age of forty-nine cases of auricular fibrillation with no other evidence of cardiac disease. The solid line indicates the age at onset, and the dotted line, the age of the patient when examined.

cardiac disease on physical examination. An interesting and possibly significant finding was the presence of premature beats between paroxysms of auricular fibrillation in 20 patients. Several patients presented slight murmurs, all systolic, mitral, pulmonic or aortic, to which no definite organic importance could be attached. Roentgen studies were performed on 18 patients at the first observation, and electrocardiographic confirmation of auricular fibrillation was obtained in 25 instances. Minor degrees of left axis deviation with angles varying from 0 to minus 15 degrees were present in 5 instances, in at least 3 of which the deviation was associated with a transverse position of the heart due to a high diaphragm.



TABLE 1 (Subgroup 1)—Data on Patients with Atrial Fibrillation with no Other Evidence of Cardiac Disease (Age at Onset Under 40 Years)

Case No.	Sex	Age at Onset	Age at Exam	Type	No. of Attacks	Duration of Attacks	Probable Precipitating Cause	Possible Contributory Factors	Diagnosed by	Years Followed	Years Since Onset	Age at Present	Follow Up	Follow Up Data*
1	M	8(?)	26	Established	3	? years	Alcohol (2)		Electro cardio gram	7	25	33	Letter	Prolonged fibrillation, converted to normal rhythm, two recurrences owing to alcohol, permanent fibrillation 1 year ago, now well, healthy, athletic, no symptoms except palpitation on exertion
2	M	14(?)	24	Established	2	? years			Electro cardio gram	6	16	30	Letter	Prolonged fibrillation, converted to normal rhythm, soon reverted to permanent fibrillation, now well, healthy, athletic, no symptoms except palpitation on exertion
3	M	18	23	Paroxysmal	3	4 to 8 days	Exertion (1) (running)	Garage work, fatigue	Electro cardio gram	2	7	25	In person	Healthy, active, athletic, no symptoms, no paroxysms for 2 years, heart normal
4	F	19	48	Paroxysmal	3	1 week to 7 year			Electro cardio gram	1	30	52	In person	Well, obese, works hard, no symptoms, no paroxysms for 2 years, heart normal, electrocardiogram showed inverted lead III
5	F	21	21	Paroxysmal	1	8 hours	Vomiting	Coryza, pregnancy	Physician	6	6	27	Letter	Excellent health, occasional palpitation from excessive smoking or strenuous exertion, no other symptoms
6	M	23	23	Paroxysmal	1	12 hours	Exertion (running)	Fatigue	Physician	11	11	34	Letter	Healthy, active, no symptoms, no paroxysms for 11 years, passed several rigid physical examinations
7	M	20	28	Paroxysmal	6	1½ to 4 hours	Emotion (fear)		Electro cardio gram	6	11	34	In person	Occasional paroxysm, otherwise healthy, active, athletic
8	M	23	25	Paroxysmal	3	16 hours to 7 months	Exertion (1)		Electro cardio gram		2			Untraced, last seen 3 years ago
9	M	24	24	Paroxysmal	10	15 minutes to hours	Exertion (1) (running)	Fatigue	Electro cardio gram	6	6	30	Letter	Excellent health, active, athletic, no symptoms save an occasional paroxysm
10	M	24	24	Paroxysmal	1	12 hours		Fatigue	Electro cardio gram	1	1	28	In person	Well, active, athletic, occasional premature beats from excessive smoking
11	M	24	24	Paroxysmal	1	24 hours		Obesity	Electro cardio gram					Untraced, last seen 2 years ago
12	M	25	35	Paroxysmal	Innumerable	½ hour to 2 days	Exertion (gymnastic work) alcohol (1)		Electro cardio gram	6	16	41	In person	Well, active, instructor in gymnastics, paroxysm every 1 or 2 months, no other symptoms, heart normal on examination and by recent roentgenogram, electrocardiogram showed short PR interval with prolonged QRS interval and left axis deviation

13 M	29	29	Paroxysmal	3	2 to 3 hours	Alcohol and vomiting (7)	Fatigue	Electro- cardio gram	0	6	35	In person	Well, active, athletic, no symptoms, heart normal on examination and by roentgenogram; electrocardiogram showed prominent P waves in leads I and II and slurred QRS waves in lead III (unchanged in 6 years)
14 M	29(?)	31	Established	1	? years			Electro cardio gram	6	8	37	In person	Well, active, athletic, no symptoms, heart normal on examination
15 M	29	44	Paroxysmal	2	2 to 4 days	Emotion (excitement)		Electro cardio gram	2 mo	15	44	In person	Health excellent, occasional palpitation at night, heart normal on examination
16 M	35	35	Paroxysmal	1	15 days	Alcohol and severe burns		Physi- cian					Died of tetanus 2 weeks after being severely burned during an alcoholic debauch, necropsy showed heart to be normal
17 M	35	35	Paroxysmal	2	5 days		Operation gas tro enteros- tomy with ether anesthesia	Electro cardio gram					First paroxysm on eighth postoperative day, second attack 1 month later, untraced, last seen 5 years ago
18 M	35	45	Paroxysmal	Innu- merable	1 hour to 2 days			Electro cardio gram	9	19	54	In person	General health fairly good, paroxysms gradually increased in frequency until permanent fibrillation became established 2 years ago. slight dyspnea on effort, heart enlarged, no murmurs, by roentgenogram, T = 15.2 cm, TH = 28.7 cm, blood pressure 180/115, electrocardiogram showed auricular fibrillation, slight deviation of the axis to the left and slurred QRS complexes
19 F	35	45	Paroxysmal	Innu- merable	1 to 2 hours			Physi- cian	5	15	50	In person	General health fair, easily fatigued, paroxysms diminishing in frequency (three yearly), heart normal on examination and by roentgenogram and electrocardiogram
20 F	37	37	Paroxysmal	Many to 24 hours	Few minutes to 24 hours	Emotion (1) (excitement)		Physi- cian	13	13	50	Letter	Health excellent, occasional paroxysm of short duration
21 M	37	39	Paroxysmal	3	10 days to (?) 3 years		Frequent respiratory infections, fatigue	Electro cardio gram	4	6			Died at 48 of meningitis (tuberculous ?), 11 years after onset of paroxysms of fibrillation, no autopsy
22 F	38	50	Paroxysmal	Innu- merable	10 to 12 hours	Pelvic abscess (1)		Physi- cian	2	14			Died at 52 of acute infection (hemolytic streptococcus) involving pharynx with probable septicemia, no necropsy
23 M	39	54	Paroxysmal	Innu- merable	5 to 24 hours			Physi- cian	12	27	66	In person	General health fair, paroxysms occur every 2 weeks, dyspnea on effort, heart enlarged on examination and by roentgenogram, T = 14.6 cm, TH = 24.6 cm, apical and aortic systolic murmurs, blood pressure 220/120, electrocardiogram showed moderate deviation of the axis to the left

\* In this and the following table, T means transverse diameter of heart and TH, internal diameter of the thorax

TABLE 2 (Subgroup 2) —Data on Patients with Auricular Fibrillation of the Paroxysmal Type with no Other Evidence of Cardiac Disease  
(Age at Onset Over 40 Years)

Case and Sex	Age at Onset	Age at When Examined	No of Attacks	Duration of Attacks	Probable Precipitating Cause	Possible Contributory Factors	Diagnosed by	Years Followed	Years Since Onset	Age at Present	Follow Up	Follow Up Data
24 M	41	41	1	Few hours	Malarial chill for treatment of syphilis of the central nervous system		Electro cardiogram	1	1	42	In person	General health good except for spells of confusion, occasional premature beats, heart normal on examination and by roentgenogram, electrocardiogram showed auricular premature beats, inverted lead III (transversely placed heart)
25 M	42	42	1	Few days		Fatigue	Electro cardiogram	2	2	44	Letter	General health fair, symptoms of neurocirculatory asthenia but no recurrence of auricular fibrillation
26 M	43	43	8	5 hours to 9 weeks		Fatigue	Electro cardiogram	12	12	55	In person	General health fair, easily fatigued, occasional pains in legs, palpitation from premature beats and an occasional paroxysm, heart normal in size, apical systolic murmur, electrocardiogram showed auricular premature beats
27 M	43	43	2	2 days to 1 week		Obesity, tobacco	Electro cardiogram	6 mo	6 mo			Followed for six months, last seen six years ago, well, had lost 30 pounds no symptoms
28 M	44	44	2	Several days			Physician	6	6	50	In person	General health good obese no symptoms, heart not enlarged, no murmurs roentgenogram showed a transversely placed heart with T = 13.8 cm, TH = 27.2 cm, electrocardiogram showed inverted lead III
29 M	44	44	Many	2 to 3 days		Respiratory infections, tobacco (1)	Electro cardiogram	10	10	54	Letter	General health good, continued paroxysms of one or two yearly, no other symptoms, heart normal on physical examination and by roentgenogram and electrocardiogram
30 M	44	46	Many	Several hours to 1 year		Nervous strain, fatigue	Electro cardiogram		2	46		Examined for first time recently
31 M	46	46	Many	Several hours	Thyrototoxicosis		Physician	8	8	54	Letter	Eight months after first observation, condition diagnosed as thyrototoxicosis thyroidectomy performed, seven years after operation, well except for occasional paroxysms
32 F	48	48	13	1 to 2 hours		Chronic bronchitis fatigue	Physician	1	1			Died at age of 52, suddenly, several weeks after attack of pneumonia, cause (?) coronary disease, no autopsy
33 M	48	53	5	3 hours to 2 days			Physician	8	13	61	Letter	General health excellent except for occasional attacks of diarrhea no cardiac symptoms, no paroxysms for years, heart normal, electrocardiogram showed PR interval to be from 0.22 to 0.24 seconds, slight left axis deviation
34 M	49	64	6	2 to 10 hours		Overeating (1)	History	2	17	66	In person	General health good, one paroxysm in past two years no other symptoms, heart normal on physical examination and by roentgenogram and electrocardiogram
35 M	52	52	12	12 hours to 2½ days			History	11	11	63	In person	General health good no paroxysm for 2½ years no symptoms, heart full sized no murmurs, roentgenogram showed T = 12.7 cm TH = 24.5 cm blood pressure 160/85 electrocardiogram showed ventricular premature beats no abnormal deviation of the axis

36 M	52	56	Innu- merable	1 hour to 2 days		Nervous strain	Electro cardiogram	7	11	63	Letter	General health fair, frequent paroxysms continue, has colitis
37 M	53	53	1	3 days		Nervousness	Physician	8	8	61	Letter	General health good, nervous, no recurrence of auricu- lar fibrillation, has occasional premature beats
38 M	53	58	Many	15 hours to 3 days			Electro cardiogram	11	16	69	In person	General health good, from two to three paroxysms yearly (17 in last seven years), chops wood, walks from 3 to 6 miles daily, no dyspnea, heart full sized, no murmurs, blood pressure 150/80, roentgenogram showed T = 12.8 cm, TII = 24.1 cm, aorta tortu- ous, electrocardiogram showed no abnormal devia- tion of the axis, inverted T wave in lead III
39 M	53	62	Innu- merable	1 to 2 hours			Physician	9	17	70	Letter	General health good, paroxysms continue but fewer and less disturbing, two years ago had prostatec- tomy, phlebitis, and pulmonary embolism with recovery
40 M	56	56	2	2+ days	Gallbladder colic		Physician	6 mo	1	57	In person	General health fairly good, occasional pain in chest and shoulder during bad weather, no recent paroxysms, no cardiac symptoms heart, blood pressure and roentgen evidence normal, electrocardiogram showed slight left axis deviation
41 M	57	60	2	48 hours to 3 months			Electro cardiogram	7	10	67	Letter	Nervous, easily fatigued, otherwise in good health, no paroxysm in past seven years
42 M	58	58	1	6 hours	Operation partial gastrectomy with ether anesthesia		Physician					Died third postoperative day (gastric carcinoma) of peritonitis, auricular fibrillation on second day, autopsy revealed heart to be normal
43 M	58	63	Innu- merable	15 minutes to 1 hour		Mild arthritis	Physician	11	16	74	In person	General health good for ten years, paroxysms continue but less frequent and less disturbing, prostate hyper- trophy, heart not enlarged, harsh apical systolic murmur, blood pressure 140/85, roentgenogram of heart normal, electrocardiogram showed low T wave in lead I, prominent T wave in leads II and III
44 M	60	62	Innu- merable	5 minutes to 12 hours		Fatigue	History	6	8	68	In person	Health fair, frequent paroxysms (1 weekly), no other symptoms, heart not enlarged, no murmurs, roent- genogram showed T = 11.6 cm, TII = 25.1 cm, electrocardiogram showed normal record
45 M	61	61	Many	1 to 5 hours	Alcohol (2), bron- chopneumonia (2)		Physician	8	8	72	Letter	Frequent paroxysms, very disturbing, with pain in left side of chest
46 M	61	61	Innu- merable	Few minutes to hours		Nervous strain, fatigue	Physician	5	6	70	Letter	Patient known to be living but exact status undeter- mined, last seen one year ago with frequent paroxysms, otherwise in good health
47 M	67	67	Many	1 hour to 4 days		Overeating (1)	Physician	9	9	76	In person	Excellent health except for indigestion and occasional paroxysms, heart normal on examination and by roentgenogram and electrocardiogram, blood pres- sure 120/70
48 M	71	71	1	1 day	Lobar pneumonia		Physician					Auricular fibrillation appeared on third day of lobar pneumonia, died on fourth day, no autopsy
49 M	75	75	1	6 hours		Acute urinary frequency and diarrhea	Physician	6	6	81	Letter	Patient known to be living, but exact status undetermined

The basal metabolic rate was normal or reduced in the 8 cases in which a test was made

*Type, Frequency and Duration*—According to type, the condition was classified as established or permanent in 3 cases in which the arrhythmia was of several years' duration without a tendency toward spontaneous cessation, and as transient or paroxysmal in 46 cases. Reference to tables 2, 3 and 4 reveals that over half the patients had few paroxysms. Great variation in the duration of paroxysms was noted, from the shortest of a few minutes to the longest lasting one year, usually the paroxysms continued a few hours or days. The 3 patients with established fibrillation thought that the irregularity had been present since childhood, 1 at the age of 8 was found by his physician to have an irregular pulse.

*Etiology*—The discoverable etiologic factors in the present group are few. As shown in tables 1 and 2, the factors have been divided into probable precipitating and possible contributory factors. In the former group are placed those factors which seemed intimately related to the onset of a paroxysm, namely, toxic (pneumonia, malarial chill, pelvic abscess, alcohol, ether), traumatic (burns) and reflex (gallbladder colic, gastric resection for carcinoma, vomiting) and those due to exertion (running, gymnastic work) and nervous strain (excitement, emotion, fear). The latter group contains less definite but possible causes, namely, fatigue, a sensitive nervous system, obesity and toxic factors such as mild infections, carbon monoxide and tobacco, in which the association was plausible but remote. In no instance when more than one paroxysm had occurred was the same etiologic factor responsible for all or even more than two paroxysms in the same person. The majority of our patients were of a nervous, "high strung" type, and a history of fatigue, mental or physical, at the time of initial or subsequent attacks was common. No conclusive etiologic relationship was found to exist between past infections or the habitual use of coffee, tea and tobacco and the occurrence of fibrillation. Undemonstrated coronary sclerosis may have been a factor in some of the older group of patients.

*Follow-Up Study*—Of the entire group of 49 patients with auricular fibrillation, 21 were followed up in person, 15 were traced by letter (from physician or patient), 6 were found to be dead, 2 are known to be living but their exact status is not known, 1 patient was seen for the first time recently and 4 could not be traced. In order to bring out any existing differences in prognosis, the younger and older patients have been segregated into two subgroups, those under and those over 40 years, according to their age at onset as determined from the history. Tables 2 and 3 give the pertinent data for each subgroup, and table 3 summarizes the present status of the patients followed up in relation to frequency of paroxysms.

**Subgroup 1** Onset in patients under 40 years of age (23 cases). In this subgroup, which includes all 3 patients with established fibrillation, 17 patients have been followed (11 in person) for periods of from four to thirty-three years since the onset, 3 are dead of various causes (to be discussed later), and 3 have not been traced. In 7 patients the paroxysms have ceased, 5 have occasional paroxysms now and 2 have frequent attacks. Except for 2 patients who have had definite cardiovascular changes, all may be said to have good health. One of the patients with established fibrillation has maintained normal rhythm for six years after at least two years of continuous fibrillation, all 3 of this group possess otherwise excellent health. Those patients with complications deserve brief mention. In case 18 the patient had had paroxysms of fibrillation for seventeen years, gradually increasing in frequency until two years ago when permanent

fibrillation became established, now at 54, though his health is fair, he has slight dyspnea on effort, cardiac enlargement, hypertension and moderate left axis deviation disclosed by electrocardiogram. The patient in case 23 had had innumerable paroxysms which occurred every two weeks, and in time moderate dyspnea, cardiac enlargement, apical and aortic systolic murmurs, hypertension and moderate left axis deviation have developed. Of the 3 deaths, one was possibly related to the heart. In case 22 the patient, a woman, died at the age of 52 years of acute hemolytic streptococcic pharyngitis, with probable septicemia, fourteen years after the first appearance of innumerable paroxysms of fibrillation. The auricles were fibrillating at the time of death, no postmortem examination was made. In the other 2 patients (cases 16 and 21) death was due to tetanus and meningitis, respectively, with normal cardiac findings at necropsy in the former.

TABLE 3—Data on the Cases of Auricular Fibrillation Showing the Relationship of the Present Status of the Patient to the Number of Paroxysms with a Comparison According to the Age at Onset

Age at Onset, Years	Number of Paroxysms	Number of Cases	Present Status of the Patient									
			Paroxysms					Complications				
			Ceased	Few	Frequent	Permanent Fibrillation	Dyspnea	Heart			Hypertension	Prolonged P R Interval
								Murmurs	Full sized	Definitely Enlarged		
Under 40	Few	9	6	3								
	Many	1		1								
	Innumerable	4		1	2	1	2	1		2	2	
	Established fibrillation	3	1			2						
	Total	17	7	5	2	3	2	1		2	2	
Over 40	Few	10	8	2			1		1		1	
	Many	5		4	1				1			
	Innumerable	4		2	2			1				1
	Established fibrillation	0										
	Total	19	8	8	3		1	1	2		2	1

Subgroup 2 Onset at over 40 years of age (26 cases) Nineteen patients had been followed up (10 in person) for intervals ranging from one to seventeen years after onset, 3 are dead, 2 are known to be living, 1 was seen for the first time recently and 1 has not been traced. In 8 patients attacks have ceased, an equal number have occasional paroxysms, and 3 have frequent attacks. Mild cardiovascular changes have occurred in 5 patients and in 1 hyperthyroidism developed. The complications that have occurred consist of mild hypertension and "full-sized hearts" in 2 patients (cases 35 and 38), a loud apical systolic murmur without cardiac enlargement in 1 (case 43), a prolonged PR interval (from 0.22 to 0.24 second) which persisted unchanged for one year in 1 (case 33) and the development of hyperthyroidism requiring thyroidectomy in 1 (case 31) eight months after he was first observed. Of the 3 recorded deaths 1 (case 32) was probably due to cardiac disease. A woman with paroxysms of fibrillation for four years dropped dead at the age of 52 on returning to work in a factory after convalescing from pneumonia, death was ascribed to coronary disease, but autopsy was not performed. In the others (cases 42 and 48) death followed peritonitis and lobar

pneumonia, respectively, in 1 case autopsy revealed a normal heart. The exact status of 2 patients known to be living has not been determined, but 1 of these (case 46) was last seen one year before this report was written, at which time he was having frequent paroxysms, though his general health was good.

**Comment.** It should be emphasized that the cardiovascular complications recorded here are present only in elderly persons years after the inception of auricular fibrillation, and in each instance there is the same fundamental pathologic background, arterial sclerosis, with differences only of degree and distribution. A certain proportion of similar changes is to be expected in any group of persons observed in the late decades of life. That the same factor is responsible for the genesis of fibrillation and for the production of cardiac complications seems unlikely except perhaps in some of those in whom fibrillation appeared well after middle age at the time when arteriosclerotic changes usually appear. Improvement, manifested by cessation of paroxysms or gradual diminution in their frequency, was shown in 66 per cent of the whole group followed. A priori, one would anticipate less improvement in the older age group, but, as demonstrated in table 4, no significant differences between the two subgroups exists.

TABLE 4—*Results of Quinidine and Digitalis Therapy in Auricular Fibrillation*

Age at Onset, Years	Quinidine					Digitals		
	Number of Patients Treated	Effective		Ineffective	Ineffective Later	Number of Patients Treated	Normal Rhythm Restored	Ineffective
		Alone	With Digitals					
Under 40	12	6	5	1	2	12	1	11
Over 40	20	17		3	3	7	2	5
Total	32	23	5	4	5	19	3	16

**Prognosis.**—On the basis of the experiences given here, the outlook for the patients with fibrillation but with no signs of cardiac disease appears good and conforms to that of the similar group followed by Parkinson and Campbell<sup>50</sup>. In striking contrast, on the other hand, are the studies reported by Stroud, LaPlace and Reisinger<sup>50</sup> and Cookson<sup>51</sup> on persons with auricular fibrillation accompanied by cardiac disease, in whom the average duration of life was from two and a half to seven years. More than half of our group with paroxysmal fibrillation showed some degree of improvement, with little tendency toward the development of the permanent form. Cessation of paroxysms was confined entirely to those patients who had had but few attacks. As would be expected, the best prognosis is held by the younger persons, in whom paroxysms have occurred infrequently. After considerable intervals the cardiovascular changes in our group have been few, rarely serious and in some instances wholly incidental to the presence of fibrillation. Hyperthyroidism was an uncommon complication. The mortality from auricular fibrillation or from cardiac disease was almost negligible.

**Treatment.**—In this series of cases of auricular fibrillation, in which the majority of patients were of a nervous, emotional temperament, constant reassurance along with general measures, namely, rest, exercise, diversion and

50 Stroud, W. D., LaPlace, L. B., and Reisinger, J. A. The Etiology, Prognosis and Treatment of Auricular Fibrillation, *Am J M Sc* **183** 48, 1932.

51 Cookson, H. The Etiology and Prognosis of Auricular Fibrillation, *Quart J Med* **23** 309, 1930.

avoidance of fatigue, nervous strain and any factors thought to precipitate paroxysms, proved helpful. Sedative drugs were useful in the very nervous patients. Quinidine was the most effective therapeutic agent and in our opinion is the drug of choice. It was used in 32 of our 49 cases, in doses ranging from 3 to 6 grains (0.195 to 0.39 Gm) from three to six times daily, and was effective in restoring normal rhythm or preventing paroxysms in 28. It became ineffective after prolonged use in 5 of these 28 cases, thus reducing its final efficacy to 72 per cent. The drug was slightly more effective in the younger than in the older age group. Much less effective was digitalis, normal rhythm returned in but 3 of 19 instances when it was used. Table 4 summarizes the results of drug therapy.

#### AURICULAR FLUTTER

The data on 7 cases of auricular flutter occurring without other manifestations of cardiac disease can be most clearly presented by means of brief summaries giving the facts of major importance in each instance.

CASE 1—D T, a man aged 27, a printing-press feeder, was first seen by us on June 30, 1926, with a history of innumerable attacks of cardiac disturbance for fifteen months, characterized by sudden rapid, regular palpitation, choking, dyspnea, weakness, dizziness and faintness, occurring on the slightest exertion and lasting from fifteen to twenty minutes, with abrupt cessation, leaving the patient weakened. Digitalis seemed to help, and with rest recently he had had fewer attacks. The past history revealed whooping cough, influenza followed by jaundice, rheumatism in the left foot (for one week years ago), sore throat and colds and recent loss of weight (16 pounds [7.3 Kg] in nine months). The patient drank coffee twice daily, and although he was formerly an inveterate smoker, he now rarely used tobacco, and he took no alcohol. Physical examination revealed tuberculosis at the apex of the left lung, no enlargement of the heart, no murmurs, a rate of 150 (slowed to 100 with orbital pressure), and a blood pressure of 125 mm of mercury systolic and 75 mm diastolic. Laboratory examination (blood, urine, stool) showed nothing abnormal. Roentgen study of the lungs revealed bilateral apical pulmonary tuberculosis, a plate taken at 7 feet (213 cm) showed the heart to be normal in size and shape, a dental film indicated absorption about the root of one molar. Several electrocardiograms showed auricular flutter, with the auricular rate varying from 250 to 292, and the ventricular rate from 60 to 275, with 1:1, 2:1, 3:1 and 5:1 rhythm. With 1:1 rhythm at auricular and ventricular rates of 275, intraventricular block of the left branch type appeared.

Treatment gave the following results: quinidine alone produced 3:1 block, digitalization produced from 3:1 to 5:1 block, and quinidine (6 grains six times daily for two days) restored normal rhythm, after sixteen days of flutter. The patient was placed in a sanatorium for six months and was then discharged with healed tuberculosis. On March 15, 1934, he was readmitted to the sanatorium with advanced pulmonary tuberculosis. Normal rhythm had been maintained for eight years, the patient had no cardiac symptoms, his heart was normal in size with no murmur, and his blood pressure was 110 systolic and 70 diastolic. It was nine years since the onset of auricular flutter.

CASE 2—C V, a woman, aged 28, a technician, first examined by us on March 29, 1923, had a history of from ten to fifteen paroxysmal attacks of cardiac disturbance beginning at the age of 16 (twelve years before). The attacks were characterized by an abrupt onset of rapid, regular palpitation, fluttering in the chest and a sensation of smothering, induced by strenuous exertion, such as playing tennis or basketball and running for a street-car, they lasted from five to ten



minutes and were relieved almost immediately by rest, after which exercise could be resumed in normal fashion. The longest paroxysm, brought on by running, lasted four hours, with spontaneous cessation. The patient's health was excellent, and she had no other symptoms of cardiac disease. The past history was entirely irrelevant except for the usual childhood diseases—measles, mumps, chickenpox and occasional tonsillitis. Tea, coffee, tobacco and alcohol were little used. Physical examination revealed nothing of importance. The heart was normal in size, there were no murmurs, the rate during a paroxysm was rapid and regular at 165 per minute, and an electrocardiogram showed auricular flutter with a 2:1 block, with the auricular rate 330 and the ventricular rate 165. During normal rhythm a normal record was obtained with a ventricular rate of 100.

For the next eleven years she enjoyed perfect health except for a carbuncle in 1925 and two or three paroxysms of tachycardia a year of from one to five minutes' duration each, similar to the duration of the proved flutter. In 1929 a basal metabolism test showed a rate of plus 4 per cent. In April 1934, at the age of 39, twenty-three years after the beginning of the attacks, the patient was perfectly healthy and played tennis and swam without cardiac embarrassment. Her heart was normal in size, rate and rhythm, with no murmurs, and the blood pressure was 125 systolic and 80 diastolic. The electrocardiogram showed normal rhythm, with a diphasic P wave in leads II and III and a flat T wave in lead III. The paroxysms have been of such short duration that no medication has been required. It was twenty-three years since the onset.

CASE 3—H. M., a salesman, aged 34, of a nervous temperament, was first seen by us on Oct. 3, 1921, with a history of premature beats for thirteen years beginning after an attack of pneumonia at the age of 21 and of innumerable attacks of rapid, usually regular, but occasionally irregular, palpitation for eight years. The attacks were accompanied by weakness, at first infrequent, but for the three years prior to examination coming every three weeks, lasting from one to three hours, and subsiding spontaneously. The paroxysm from which he sought relief had been present constantly for six weeks. No precipitating cause for the paroxysms was apparent. The past history revealed diphtheria in childhood, pneumonia, jaundice at 25, influenza at 31 and occasional sore throat. Coffee and tobacco were used in moderation. Three years before he was first observed by us he qualified for life insurance. Physical examination by us revealed little that was abnormal, the heart was not enlarged, the apex impulse being in the fifth space 7 cm. to the left of the midsternum and within the midclavicular line, there were no murmurs, the sounds were rather weak, and the rhythm was rapid and irregular, the blood pressure was 135 systolic and 90 diastolic, there was slight edema of the left leg from varicosities, but there was no evidence of congestive failure. Several electrocardiograms taken over a two week period showed auricular flutter with auricular rates from 305 to 310 and ventricular rates from 90 to 155, with changing auriculoventricular block varying from 2:1 to 5:1. On digitalis therapy little improvement was noted, but with 28 grains (2.42 Gm.) of quinidine in divided doses in one day normal rhythm was restored after eight weeks of constant flutter. The electrocardiogram made after this treatment gave normal results.

For the next five years the patient had frequent paroxysms lasting several hours, usually at night, each responding favorably to 6 grains of quinidine. The paroxysms were apparently more frequent during periods of mental stress. He was last heard of by us in July 1931, when he was admitted to a hospital with phlebitis of an extremity and pulmonary embolism. He had continued to have frequent attacks of palpitation, and slight substernal distress on exertion, not thought to be angina pectoris, had developed. Enlargement of the left ventricle

was evidenced on roentgen study, and an electrocardiogram revealed auricular fibrillation. The blood pressure was normal. An electrocardiogram made after normal rhythm had been restored with digitalis and quinidine revealed a prolonged PR interval (0.26 second) and ventricular premature beats. Since his discharge in 1931 the patient's fate has been unknown to us, efforts to follow him have been unsuccessful. The patient was followed for eighteen years after the onset.

CASE 4—W. R., a lawyer aged 40, first seen by us on March 11, 1932, had a history of premature beats for six months present only with a cardiac rate below 100, this was first noted by his wife (formerly an anesthetist), for the patient was unaware of them subjectively. He had had no symptoms of cardiac disease, and his exercise tolerance was normal. The past history revealed none of the common infectious diseases. For one year he had been under treatment for syphilis of the central nervous system in the early stage, and consultation for an opinion on the condition of his heart was requested during treatment with malaria. Five years previously, at 35, he passed an examination for life insurance. Tea, coffee and alcohol were used moderately, but tobacco was used in larger amounts (from four to five cigars daily). The patient's health had been excellent except for the aforementioned disturbance. Physical examination (three hours after a malarial chill) revealed a well developed and well nourished man who was clear mentally but concentrated with difficulty. The pupils were fixed to light, and slight arcus senilis was present. The heart was of normal size, with fair sounds and no murmurs. The rhythm was irregular owing to frequent premature beats, at a heart rate of 86. The blood pressure was 105 systolic and 70 diastolic. Following a malarial chill with high fever the heart rate was found to be very rapid, and an electrocardiogram taken on March 12, 1932, showed auricular flutter, an auricular rate of 300 and a ventricular rate of 140, with 2:1 and 3:1 block. After 10 grains (0.65 Gm.) of quinine was given for the malaria the flutter of several hours' duration ceased. The electrocardiogram then showed auricular and ventricular extrasystoles.

One year later (in July 1933) the patient was seen again under similar circumstances in the hospital with auricular fibrillation (detected by electrocardiogram) following combined malarial and typhoid vaccine therapy for the syphilis. In April 1934 he was in good health except for occasional symptoms of disturbance of the central nervous system (spells of confusion), he was working hard and smoking heavily. He had occasional premature beats but no cardiac symptoms. His heart was normal in size and rate, with premature beats but no murmurs. The blood pressure was 115 systolic and 75 diastolic. The electrocardiogram showed auricular premature beats and total inversion of lead III, with slight slurring of the QRS waves in lead II. Fluoroscopic examination of the heart revealed a transverse normal heart and a normal aorta. It was two years since the onset.

CASE 5<sup>52</sup>—E. J., a machinist aged 49, first seen by us on July 16, 1924, had a history that two years before, while running for a street-car, rapid fluttering of the heart began, accompanied by choking sensation, dizziness, faintness and some precordial distress. Improvement followed the initial attack, but palpitation recurred on slight exertion and lasted from thirty minutes to one hour (presumably from the assumption of 1:1 rhythm). Two months after the onset the patient was forced to stop work because of the frequency of the distressing palpitation. The past history revealed measles, mumps and scarlet fever in childhood and a hemorrhoidectomy at 48. The patient had otherwise enjoyed good health.

52 Case 5 was previously reported by Sprague and White.<sup>40</sup>

and once had been a professional baseball player. Physical examination revealed a slender man with a hydrocele. The apex impulse and left border of dulness of the heart were in the fifth space 9 cm to the left of the midsternal line and just beyond the midclavicular line (8.5 cm), the sounds were of good quality, there were no murmurs, the rate was from 120 to 150, and the blood pressure was from 100 to 125 mm of mercury systolic and from 76 to 80 diastolic. Examination of the blood and urine and Wassermann tests yielded normal results. The basal metabolic rate was minus 9. Roentgenograms showed slight increase in the transverse diameter of the heart (probably due to dilatation from prolonged flutter) and slight torsion of the aorta. An electrocardiogram showed auricular flutter with 2:1 block, an auricular rate of 240 and a ventricular rate of 120. After exercise a 1:1 rhythm was noted, with both the auricular and the ventricular rate 240 and aberrant ventricular complexes (from intraventricular block). Digitalis and quinidine in large dosage failed to restore normal rhythm.

On Nov. 11, 1927, for reasons unknown, after five years of continuous flutter, normal rhythm returned spontaneously, bringing great relief to the patient. In January 1934, at the age of 59 years, twelve years after the onset and seven years after the offset of the auricular flutter, the patient enjoyed excellent health, having had no symptoms referable to his heart since the cessation of the flutter. The apex impulse and left border of dulness were 7.5 cm to the left of the mid-sternum (no enlargement), there were no murmurs, the rate was 72, and the rhythm was regular. The blood pressure was 120 systolic and 75 diastolic. An electrocardiogram revealed normal rhythm with slurred S waves and flat T waves in lead III, it was essentially normal. It was twelve years since the onset.

CASE 6—W. H., a retired business man aged 54, first seen by us on March 7, 1922, had a history of attacks for fifteen years consisting of rapid heart rate, usually regular but also irregular at times, accompanied by weakness, faintness and dull precordial ache, appearing every few days and lasting from a few minutes to five or six hours, with abrupt onset and offset. There was no known provoking cause of the paroxysms. One attack had been stopped by ocular pressure. The past history revealed no serious illnesses; the patient's general health had been good. He smoked moderately. Physical examination revealed nothing of importance except tachycardia. The heart was not enlarged, the sounds were faint, there were no murmurs, the rate was about 240, the blood pressure was 115 systolic and 80 diastolic (later with normal rhythm), and there was no congestion. An electrocardiogram showed auricular flutter with 1:1 rhythm, both the auricular and ventricular rates being 255. With quinidine sulphate therapy (12 grains) normal rhythm was restored after nine hours of flutter, which at times on physical examination had given very irregular cardiac rhythm, suggesting changing degrees of block or auricular fibrillation. An electrocardiogram made during normal rhythm showed a rate of 70, with slight left axis deviation (angle minus 15 degrees).

For the next twelve years the patient was observed at intervals. He had frequent paroxysms of mostly irregular palpitation (undoubtedly auricular fibrillation), though at times it was regular, every ten days or two weeks, lasting from ten to twenty-four hours, coming most frequently at night. The attacks were relieved by quinidine at first, later this drug proved ineffective in controlling the attacks and was voluntarily discontinued. Digitalis was ineffective also. In April 1934, at the age of 66, twenty-seven years after the first attack, the patient continued to have frequent paroxysms, his general health was fairly good though there was some dyspnea on exertion, his heart was slightly but definitely enlarged with slight apical and aortic systolic murmurs and an accentuated aortic second

sound, and the blood pressure was 220 systolic and 120 diastolic. Orthodiagraphy showed the heart and aorta to be enlarged (transverse cardiac diameter, 14.6 cm, internal thoracic diameter, 24.6 cm). An electrocardiogram showed normal rhythm with moderate left axis deviation. It was twenty-seven years since the onset.

CASE 7—G. H., a broker aged 66, was first seen in consultation by us on July 29, 1930, because of auricular flutter. He had always been strong, well and active but had been under great nervous strain for one year. Two weeks before examination a gangrenous appendix had been removed, and the area was successfully drained. On the eighth postoperative day the patient had transient sharp but not severe precordial pain, which was relieved at once by belching gas. On the ninth day a rapid irregular pulse was discovered which proved by electrocardiogram to be due to auricular flutter with an auricular rate of 320 and a ventricular rate of 100 to 120 with 2:1 and 4:1 block. Digitalization converted the rhythm to normal after four days of flutter. Prior to this paroxysm the patient had not had cardiac symptoms. Physical examination revealed nothing of importance except for the surgical wound. The heart was not enlarged, the sounds were fair in quality and rather soft, there were no murmurs, the rate and rhythm were normal, and the blood pressure was 130 systolic and 80 diastolic. The urine was normal. A second electrocardiogram, made three days after the first, showed auricular premature beats with slightly low voltage.

In December 1931 the patient was successfully operated on for fracture of the head of the femur. The heart was normal at that time. In 1934, at the age of 70, four years after the first and only paroxysm of auricular flutter, he was well except for mild arthritis, he played eighteen holes of golf, and aside from slight dyspnea on climbing hills he had no symptoms. His heart was of normal size, the sounds were good, there were no murmurs, and the blood pressure was 140 systolic and 85 diastolic. Fluoroscopic examination revealed an apparently normal heart and aorta. An electrocardiogram showed auricular premature beats, a rate of 75, no abnormal axis deviation and normal T waves.

### SUMMARY

1 *Auricular Fibrillation in Patients Without Other Evidence of Cardiac Disease*—We have presented observations on 49 patients in whom auricular fibrillation occurred without other signs of cardiac disease. The ages varied from 21 to 75 years. All save 3 cases were of the paroxysmal type, few paroxysms occurred in 46 per cent of these. Definite etiologic factors were few, but instances have been presented in which the appearance of fibrillation was related to pneumonia, malarial chill, pelvic abscess, alcohol, ether, burns, gallbladder colic, vomiting, surgical operation, exertion and emotion (excitement and fear). Follow-up studies on 90 per cent of the entire group revealed 1 probable death from cardiac disease four years after the onset of paroxysms of auricular fibrillation, 6 patients with cardiovascular complications which had appeared some years after the first auricular fibrillation and 1 patient in whom hyperthyroidism had developed. The essential data have been recorded briefly, and a comparison of the follow-up results, with respect to age at onset, has been made. The prognosis for life and

for the maintenance of adequate cardiac function is with rare exceptions excellent, and the outlook for improvement in the number of paroxysms is also good. We regard reassurance, the avoidance of exciting factors and the use of quinidine sulfate as the most useful therapeutic measures, quinidine sulfate was consistently effective in 72 per cent of the patients of the present group to whom it was given.

*2 Auricular Flutter in Patients With No Other Evidence of Cardiac Disease*—The histories of 7 patients with auricular flutter in whom the disorder was unaccompanied by other manifestations of cardiac disease have been reported briefly. The ages ranged from 27 to 66 years. 4 patients were 40 years old or younger when first seen by us. All attacks were paroxysmal, the number of paroxysms varying from one in 3 instances to innumerable attacks in the remainder. The duration of individual paroxysms was from a few minutes to five years, but usually several hours. Electrocardiographic proof of flutter was obtained in each patient. The common symptoms were palpitation (rapid, usually regular), choking, dyspnea, dizziness, faintness, weakness and, occasionally, precordial pain. The precipitating factor was clearly exertion in 3 cases, in 1 flutter followed a therapeutic malarial chill, and in another it appeared after the removal of a gangrenous appendix with the patient under ether anesthesia. Coffee, tea, tobacco and alcohol played no apparent etiologic rôle in these cases. Six patients have been followed up for from two to twenty-seven years after the onset, five are entirely well at the time of writing, and the remaining patient (case 7), at 66, after twenty-seven years, has some dyspnea, cardiac enlargement, apical and aortic systolic murmurs and hypertension but no signs of congestive failure. The seventh patient (case 3) was last seen eighteen years after his first attack, when he had frequent paroxysms of auricular fibrillation and roentgen study showed slight enlargement of the left ventricle. Quinidine, or its isomer quinine (case 4), was used alone in 5 cases, being effective in restoring normal rhythm or preventing paroxysms in 3 and later proving ineffective in 1 of these. Digitalis restored normal rhythm in 1 of 5 cases in which it was tried. Quinidine after digitalization converted the rhythm to normal in 2 instances.

### CONCLUSIONS

Paroxysms of auricular fibrillation and of auricular flutter occur not infrequently in persons with no other signs of cardiac disease.

Follow-up studies on 54 patients of the present series (47 with auricular fibrillation alone, 5 with auricular flutter alone and 2 with both) revealed after the lapse of a significant number of years a low mortality rate, little important cardiac disease and but a single instance of hyperthyroidism.

The prognosis for life and for the maintenance of adequate cardiac function is good

The outlook for future improvement, manifested by a decrease in frequency or complete cessation of paroxysms, is frequently good

Thus, auricular fibrillation and auricular flutter are in some persons merely exaggerated functional disorders of the heart, no more indicative of cardiac disease or of a poor prognosis than are premature beats or auricular paroxysmal tachycardia

NOTE—Since the preparation of this paper, an article by Friedlander and Levine<sup>53</sup> has appeared with a report of cases of auricular fibrillation and auricular flutter without evidence of organic cardiac disease. Through their courtesy we find that cases 15, 2 and 7 of their series are the same as cases 1, 9 and 28 of the present series of auricular fibrillation

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53 Friedlander, R. D., and Levine, S. A. Auricular Fibrillation and Auricular Flutter Without Evidence of Organic Heart Disease, *New England J. Med.* **211** 624, 1934

# MENINGITIS DUE TO TYPE I PNEUMOCOCCUS

## REPORT OF A CASE WITH RECOVERY DUE TO SERUM THERAPY

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Until recent years, recovery from pneumococcic meningitis was such a rare and exceptional event that the disease was generally regarded as fatal Kolmer<sup>1</sup> Schottmuller<sup>2</sup> and Jochman<sup>3</sup> reported a mortality of 100 per cent, while Lubarsch<sup>4</sup> and Frankel<sup>5</sup> estimated the mortality as 99 per cent and 98 per cent, respectively The first report of recovery was made by Jemma<sup>6</sup> in 1896 By 1911, only seven cases with recovery had been reported<sup>7</sup> In 1923, Halle<sup>8</sup> reported one recovery following the use of antipneumococcus serum plus fixation abscess, and in the same year Netter and Cesari<sup>9</sup> reported a recovery due to the same treatment In their report, for the first time, the type of pneumococcus was given In 1928, Harkavy<sup>10</sup> and Globus and Kasanin<sup>11</sup> reported single cases and made a partial survey of the literature, describing seven cases in addition to their own<sup>12</sup> One of the patients recovered spontaneously,

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From St Margaret's Hospital

1 Kolmer, J A Therap Gaz **44** 697 (Oct) 1920

2 Schottmuller, quoted by Steinbrink, O Beitrag zur Heilbarkeit der Pneumokokken Meningitis, Therap d Gegenw **71** 188, 1925

3 Jochman, quoted by Steinbrink, O Beitrag zur Heilbarkeit der Pneumokokken Meningitis, Therap d Gegenw **71** 188, 1925

4 Lubarsch, quoted by Harkavy<sup>10</sup>

5 Frankel, E, quoted by Harkavy<sup>10</sup>

6 Jemma Blumgarten's Jahresberichte, 1896

7 Rolly, F Deutsche med Wchnschr **37** 774, 1911

8 Halle, J Bull et mem Soc med d hop de Paris **47** 757 (May 25) 1923

9 Netter, A, and Cesari, C Bull et mem Soc med d hop de Paris **47** 763 (May 25) 1923

10 Harkavy, J Pneumococcus Meningitis Recovery with Serum Therapy, J A M A **90** 597 (Feb 25) 1928

11 Globus, J H, and Kasanin, J I Pneumococcus (Type IV) Meningitis Report of a Case Treated by Forced Subarachnoid Drainage, with Recovery, J A M A **90** 599 (Feb 25) 1928

12 (a) Parkinson, P J A Case of Postbasal Meningitis Due to Pneumococcus Lanceolatus, Brit J Child Dis **1** 112, 1904 (b) Culper, R C Primary Cryptogenic Pneumococcus Cerebrospinal Meningitis, with a Report of Three Cases, M Rec **68** 815, 1905 (c) Cumming, J H A Case of Pneumococcus Cerebrospinal Meningitis, Lancet **2** 1924, 1912 (d) Rosenow, G Heilung der Pneumokokken Meningitis durch Optochin, Deutsche med Wchnschr **46** 9 (Jan 1) 1920 (e) Campbell, J Pneumococcus Meningitis, Lancet **1** 54, 1925 (f)

(Footnote continued on next page)

in the others recovery followed treatment with subarachnoid drainage, pneumococcus serum, pneumococcus vaccine or ethylhydriocupreine hydrochloride. In none of these cases was the type of pneumococcus specified. In Harkavy's case the condition was due to type I pneumococcus, and in Globus and Kasanin's case it was due to type IV pneumococcus. From the literature I have been able to gather reports of only eight cases of pneumococcic meningitis of specified types in which recovery has taken place.<sup>13</sup> To this group I wish to add a case of meningitis due to the type I pneumococcus following a fracture of the skull, in which recovery followed the intravenous and subarachnoid injection of large quantities of Felton's antipneumococcus serum of types I and II.

#### REPORT OF A CASE

*History*—A W, a man aged 28, was admitted to St Margaret's Hospital on Dec 23, 1932, after an automobile accident in which he received an extensive laceration of the occipital region of the scalp with an inverted U-shaped fracture of the occipital region of the skull. When he entered the hospital, he seemed fully conscious except for loss of memory of the events of the night of the accident. Through the wound the fracture of the occipital region was easily palpated and was examined carefully for leakage of cerebrospinal fluid, but there was none. There was a small amount of bleeding from the nose and a hemorrhage into the left ear drum. Roentgen examination revealed the fracture in the occipital region but showed no fracture at the base of the skull. The scalp wound was sutured, with drainage, and the patient was given the usual dose of tetanus antitoxin.

*Course*—The drain was removed on the second day after the accident, and the occipital wound was watched carefully for leakage of the spinal fluid, but it remained dry throughout and healed by first intention. Four days after the accident the bleeding from the nose stopped and was followed by a continuous dripping of spinal fluid. Every effort was made to prevent the patient from blowing his nose for fear of forcing bacteria into the cranial cavity, but on the sixth day, being in a state of mental confusion, he blew his nose and at once complained of a generalized intense headache. Within a few hours his temperature had risen to 103 F, his neck was stiff, and the white cell count was 40,000, with 95 per cent polymorphonuclears. A lumbar puncture yielded cloudy spinal fluid with 100 per cent of the cells polymorphonuclears but with no bacteria. A diagnosis of men-

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Ratnoff, H L, and Litvak, A M. Pneumococcus Meningitis Treated with Morgenroth's Optochin Hydrochloride, *Arch Pediat* **43** 466 (July) 1926. (g) Brown, A C. Pneumococcal Meningitis with Recovery, *Lancet* **2** 519 (Sept 16) 1916. (h) Ervin, C E. Pneumococcus Cerebrospinal Meningitis with Recovery, *Atlantic M J* **28** 590 (June) 1925.

13 (a) Bedell, C C. Pneumococcic Meningitis. Report of a Case with Recovery Following Cisternal Drainage, *J A M A* **102** 820 (March 17) 1934. (b) Reveno, W S, and McLaughlin, N. Pneumococcus Meningitis. Recovery with Felton's Serum, *Ann Int Med* **7** 1026 (Feb) 1934. (c) Synge, V M. Pneumococcal Meningitis, *Lancet* **1** 761 (April 10) 1926. (d) Weinberg, M H. Case of Pneumococcus (Type III) Meningitis Treated with Potassium Permanganate—Recovery, Plea for Its Trial, *J Nerv & Ment Dis* **74** 38 (July) 1931. Netter<sup>9</sup> Ratnoff<sup>12f</sup> Harkavy<sup>10</sup> Globus and Kasanin<sup>11</sup>



ingitis was made, and two days later, when the lumbar puncture was repeated, pneumococci were found. Without waiting for the determination of the type of the organism, treatment was started at once, using Felton's concentrated antipneumococcus serum of types I and II. Table 1 shows the plan of treatment that was followed.

After the first intravenous injection of serum, there was a chill followed by a rise in temperature to 105 F. The temperature was irregular, ranging between 97 and 103.6 F, until the ninth day after treatment was begun, then there began a gradual fall, which continued until the thirteenth day, when the temperature reached normal. For the succeeding week the temperature was subnormal. With the onset of meningitis the pulse became slow, the rate varying between 56 and 66, and at times it was weak and irregular. The blood pressure, which had been normal between the time of the accident and the onset of the meningitis, rose to 175 systolic and 107 diastolic on the fifth day of the infection and had dropped to

TABLE 1—*Summary of Treatment Followed*

Day of Treatment	Serum Administered Intravenously, Units	Serum Administered Intraspinaly, Units	0.5% Acriflavine Hydrochloride, Cc
1	10,000 10,000 10,000		
2	20,000 20,000 20,000	10,000	20 40
3	15,000 15,000	10,000 10,000	30
4	30,000	10,000	
5	20,000	10,000	
6			
7	10,000		
Total	180,000	50,000	90

140 systolic and 95 diastolic on the fourteenth day. The white cell count, which had been 11,000 with 74 per cent polymorphonuclears two days before the onset of meningitis, rose to 40,000 with 96 per cent polymorphonuclears when the meningitis began and dropped gradually until the fifteenth day when it reached 15,000 with 76 per cent polymorphonuclears.

On the day on which treatment was begun, the spinal fluid was cloudy, with 100 per cent of the cells polymorphonuclears and with pneumococci in the smear. With each intraspinal injection, 10 to 20 cc of spinal fluid was removed. By the fourth day of treatment the pressure had become normal and bacteria rare. By the fifth day the bacteria found in the smear were gram-negative, though similar in morphology to the pneumococcus. They were interpreted as being degenerated organisms. The culture at that time was sterile.

The organism isolated in the spinal fluid was a gram-positive, lancet-shaped, encapsulated diplococcus, which grew slowly on ascitic dextrose broth. It was soluble in bile and became agglutinated in type I pneumococcus serum, and after being dissolved in bile it could be precipitated from solution by type I pneumococcus serum.

*Neurologic Symptoms*—After the accident the patient remained drowsy, being irrational at times and unable to recall the events following the accident. His mental condition improved gradually until the onset of meningitis, when he was stuporous most of the time but maniacal for short intervals and cried with the severity of the pain in his head. The neck became rigid and remained so for a week, after which it gradually relaxed. For about two weeks he remained incontinent of urine and feces. The pupils became widely dilated and ceased to react to light. On the fifth day of infection the knee jerk was absent on the left, but there was no other disturbance in reflexes and no paralysis throughout the illness. By the fifth day of treatment the Kernig sign could not be elicited, and he was rational for brief periods during the day. On the twentieth day after treatment was begun, he was rational the greater part of the time, he was able to walk on the twenty-fourth day and appeared mentally normal on the twenty-sixth day.

*Recovery*—Following the illness he made a complete recovery except for ocular and certain mental disturbances. The pupils remained dilated and fixed, reacting only slightly to brilliant light but normally to accommodation. Both optic disks were hazy, with slight pallor of the right disk and choroidal pigmentation on the temporal side of the disk. There was a loss of vision in the lower half of the visual field on the right side, and a concentric contraction of the field of vision on the left. In the right eye vision was 20/200, which was corrected with lenses to 20/50, with the left eye the patient could count fingers at 6 feet (18 meters), and with correction vision was 20/30.

Since his recovery from his illness the patient shows no change in personality, with the possible exception of a decrease in stability and reliability. He had always used alcoholic beverages in moderately large quantities, and he imbibes more freely now than before. He has been unable to stick at a job very long because of his free use of alcohol, which may or may not be a result of his injury and infection.

It was suggested by certain of my colleagues at the time of his recovery from the infection that late complications, such as abscess or recurrence of the infection, should be expected. For this reason the patient has been observed for two years, but no recurrence of symptoms has been noted.

#### COMMENT

The patients who have recovered from pneumococcic meningitis varied in age from 17 months<sup>14</sup> to 57 years, but most of them were vigorous young adults. The sexes were almost equally affected, with a slight preponderance of men.

*Source of the Infection*—Pneumococcic meningitis may follow pneumonia, infection of the upper respiratory tract, otitis media, mastoiditis, abortion<sup>12d</sup> or a fracture of the skull involving the sinuses or the cribriform plate. I have observed one case, with fatal termination, in which the infection took place through a wound of the scalp due to a kick by a mule which caused a depressed fracture of the skull and laceration of the dura.

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<sup>14</sup> Ames, J. W. Pneumococcic Meningitis. Report of Case with Recovery, Colorado Med 28 361 (Aug.) 1931.

*Type of Organism*—Bauer and St. Clair<sup>15</sup> have studied the type of pneumococci found in the spinal fluid with reference to the source of the infection. Combination of their figures with those from the nine cases in which recovery was reported gives a fair idea of the relation between the source of infection and the type of organism.

*Mode of Onset*—The onset of the disease is rapid and at times sudden, accompanied by mild or severe headache, rigidity of the neck and a rise in temperature to from 102 to 106 F, occasionally accompanied by chills. Vomiting is frequently encountered at the onset and may be violent and projectile. There may be drowsiness, stupor or coma, with periods of delirium. Convulsions are rare. Incontinence of urine and feces may occur. As the disease progresses, the neck becomes more rigid and at times is retracted, and there may be slight opisthotonos. The Kernig sign is generally present. There may be photophobia. The pupils may be contracted or dilated widely. The

TABLE 2—*Type of Pneumococcus and Source of Infection in Twenty-One Cases of Pneumococcal Meningitis*

Source of Infection	Type I	Type II	Type III	Type IV
Otitis media			4	1
Sinusitis	3			3
Fractured skull	2			2
Pneumonia, late			1	
Source obscure	1			
Infection of upper respiratory tract	1			

fundus is generally congested, and there may be optic neuritis. Paralysis of the external or of the internal rectus muscles is sometimes encountered. Reaction of the pupils to light is usually present but sluggish. The knee jerks are generally diminished or absent but are occasionally hyperactive. A Babinski sign is rarely found.

*Pulse*—The pulse is frequently relatively slow. Bedell's patient<sup>13a</sup> had a pulse rate of 94 with a temperature of 106 F, Clark's patient<sup>16</sup> had a pulse rate of 64, and my patient at the onset had a pulse rate varying between 56 and 66. Less frequently the pulse is rapid. An elevation in blood pressure has been rarely reported, though in my case it reached 175 systolic and 105 diastolic.

The white cell count is always elevated, with an increase in the percentage of polymorphonuclears, the average count being around 25,000 with 85 per cent polymorphonuclears.

<sup>15</sup> Bauer, J. T., and St. Clair, H. *Pneumococcus Types in Acute Mastoiditis and "Primary" Pneumococcus Meningitis*, J. A. M. A. **90** 1429 (May 5) 1928.

<sup>16</sup> Clark, J. G. *Recovery from Pneumococcal Meningitis*, Lancet **2** 1330 (Dec. 17) 1932.

*Treatment*—Spontaneous recovery without any treatment has been reported by Parkinson<sup>12a</sup> Weinberg<sup>13d</sup> reported a case of meningitis due to the type III pneumococcus in which recovery followed the rectal instillation of dilute potassium permanganate solution Stoessinger<sup>17</sup> reported a recovery following the intravenous and intraspinal injection of mercurochrome Brown<sup>12g</sup> treated his patient with pneumococcus vaccine While single recoveries following the aforementioned methods of treatment are reported, the largest number of recoveries have resulted from one or more of the following methods of treatment sub-arachnoid drainage, administration of concentrated antipneumococcus serum and administration of ethylhydrocupreine hydrochloride

Subarachnoid drainage through lumbar puncture without other therapeutic measures has been used successfully by Culper,<sup>12b</sup> Clark<sup>16</sup> and Uhr<sup>18</sup> Drainage by the cisternal route may become necessary owing to the fact that adhesions form at the site of the puncture and prevent drainage from the spine Concentrated antipneumococcus serum of the Huntoon or Felton type has been given intramuscularly, intravenously, intraspinally and even into the cisterna magna Almost invariably this method of treatment is combined with subarachnoid drainage of some form Rosenow<sup>12d</sup> and Ratnoff and Litvak<sup>12f</sup> have reported recoveries following treatment with ethylhydrocupreine hydrochloride, and in the opinion of the latter authors, small doses of this drug markedly increase the efficacy of the antipneumococcus serum Kolmer has stressed the advantage of the intracarotid method of injection and has outlined beautifully the details of treatment He also discussed the use of acriflavine base and Pieg'l's solution Shuller<sup>19</sup> has also summarized the methods of treatment, in an article reviewing the literature

It seems from a study of the small number of cases available that the ideal method of treatment of meningitis due to type I or type II pneumococci consists of adequate doses of pneumococcus serum combined with a small amount of ethylhydrocupreine hydrochloride injected into the subarachnoid space and into a superficial vein or the carotid artery plus adequate subarachnoid drainage by lumbar puncture as long as it is feasible and by cisternal puncture if adhesions prevent drainage by the former method<sup>20</sup> It is essential that the amount of serum be

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17 Stoessinger, H N Recovery from Pneumococcus Meningitis, *Brit J Child Dis* **27** 35 (Jan-March) 1930

18 Uhr, J S Pneumococcus Meningitis Report of Case in New-Born Infant, with Recovery, *Arch Pediat* **46** 121 (Feb) 1929

19 Shuller, E H Pneumococcic Meningitis Case Reports with One Recovery, *J Oklahoma M A* **25** 137 (April) 1932

20 Kolmer, J A Newer Methods for the Prophylaxis and Treatment of Meningitis with Special Reference to Streptococcus and Pneumococcus Meningitis, *Laryngoscope* **42** 12 (Jan) 1932

ample Harkavy's patient received 95 cc of Felton's antipneumococcus serum intravenously, 65 cc intraspinally and 30 cc into the cisterna magna Raveno and McLaughlin gave 90,000 units intravenously, 10,000 units intraspinally and 20,000 units into the cisterna magna My patient received 180,000 units intravenously and 50,000 units intraspinally

The chances of successful specific therapy in cases of meningitis type III or group IV pneumococci seem much less than in cases in which the condition is due to organisms of type I or II In these cases adequate subarachnoid drainage plus the intracarotid injection of ethylhydrocupreine hydrochloride, acriflavine base and Pregl's solution is probably the best method of treatment available Surgical cleansing of an infected mastoid or sinus is obviously essential

#### CONCLUSION

Another case of recovery from pneumococcic meningitis is added to the small but ever increasing list in the literature The organism, a type I pneumococcus, gained entrance to the central nervous system through a fissure in the cribriform plate The patient received the largest amount of pneumococcus serum yet recorded and recovered with residual symptoms in the eyes only Sterility of the spinal fluid was obtained five days after the beginning of treatment Follow-up over a period of two years has revealed no recurrence of symptoms due to the infection

# NEW FORMULAS FOR PREDICTING BASAL METABOLIC RATE FROM PULSE RATE AND PULSE PRESSURE

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AND

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In their classic descriptions of thyrotoxicosis a century ago, Graves and Basedow each recorded tachycardia as a major manifestation of the syndrome. Eighty years later, when clinical calorimetry became established as a laboratory aid in the diagnosis of exophthalmic goiter, it was discovered that a relationship existed between the pulse rate and the metabolism. Benedict commented on this parallelism in his early reports, and in 1920 Sturgis and Tompkins<sup>1</sup> published a study of the correlation between the pulse rate and the basal metabolism in cases of hyperthyroidism. That this relationship is not peculiar to thyroid disease but is associated with the consumption of oxygen was shown by Minot and Means<sup>2</sup>. These workers studied the basal metabolic rate and pulse rate in a series of patients with leukemia and in a series of patients with thyrotoxicosis, and demonstrated that in both conditions the pulse rate varied with the consumption of oxygen. The persistent parallelism between the pulse rate and the metabolism led Benedict<sup>3</sup> to say

The intimate relationship between the mechanism of the circulatory system and the total metabolism has been frequently pointed out in publications from the Nutrition Laboratory. The heart rate is, with the same individual, a remarkably significant index of the total metabolism. When it is considered that the CO<sub>2</sub> production is directly proportional to muscular activity and heat production, and furthermore, that the blood must carry away the CO<sub>2</sub> and supply fresh oxygen to the tissues, in proportion to the need therefor, it is not surprising that the work of the heart bears a general relationship to the total metabolism. If the systolic discharge from the heart were uniform under all conditions one could predict that the pulse rate would be proportional to the total metabolism. Such a pro-

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1 Sturgis, C C, and Tompkins, E H. A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, *Arch Int Med* **26** 467 (Oct) 1920

2 Minot, G R, and Means, J H. The Metabolism-Pulse Rates in Exophthalmic Goiter and in Leukemia, *Arch Int Med* **33** 576 (May) 1924

3 Benedict, F G, Miles, W R, Roth, P, and Smith, H M. Publication 280, Carnegie Institution of Washington, 1919

portionality of relationship, however, is by no means established or to be inferred from experimental evidence thus far obtained

Since the foregoing statement was written, the relationship between the total metabolism and the flow of blood has been the object of many investigations. Clinical studies of the pulse rate and the blood pressure have revealed a fairly constant parallelism between the consumption of oxygen and these two indicators of circulatory activity. More exact laboratory studies utilizing the several methods subsequently developed for measuring the flow of blood in man have added experimental evidence which indicates that the flow varies directly with the consumption of oxygen. After the degree of relationship between these variable functions of the body was established it became possible to estimate metabolism from circulatory activity.

#### PREVIOUS METHODS OF DERIVING PREDICTION FORMULAS

By utilizing measurements of the parallel functions of the consumption of oxygen and circulatory activity, one of us<sup>4</sup> in 1922 published a formula for predicting the basal metabolic rate from the pulse rate and pulse pressure. An improved formula derived from a larger series of observations was reported in 1924.<sup>5</sup> The Gales<sup>6</sup> in England endeavored to improve and simplify the formula and in 1931 suggested the equation  $BMR = PR + PP - 111$ . The following year Jenkins<sup>7</sup> published prediction tables, constructed from separate formulas for males and females, derived from his own data.

To what extent the various formulas have been utilized it is impossible to estimate, although various reports in the past decade indicate that they have found a place in clinical medicine. Within the last two years twenty reports<sup>8</sup> have emanated from workers in Europe and the

4 Read, J. M. Correlation of Basal Metabolic Rate with Pulse Rate and Pulse Pressure, *J. A. M. A.* **78** 1887 (June 17) 1922.

5 Read, J. M. Basal Pulse Rate and Pulse Pressure Changes Accompanying Variations in the Basal Metabolic Rate, *Arch. Int. Med.* **34** 553 (Oct.) 1924.

6 Gale, A. M., and Gale, C. H. Estimation of the Basal Metabolic Rate, *Lancet* **1** 1287 (June 13) 1931.

7 Jenkins, R. L. Basal Metabolism. II. The Basal Pulse Complex, *Arch. Int. Med.* **49** 188 (Feb.) 1932.

8 Umber, F. *Deutsche med. Wchnschr.* **58** 1279 (Aug. 12) 1932. Habs, H. *ibid.* **59** 333 (March 3) 1933. Bertheau, H. *Munchen med. Wchnschr.* **80** 453, 1933. Hartleben. *ibid.* **80** 1013, 1933. Kemeny, E. *Wien klin. Wchnschr.* **46** 617, 1933. Bernhardt, H. *Med. Welt* **7** 581 1933. Rosenberg, M. *ibid.* **7** 184, 1933. Olmes, H. *Klin. Wchnschr.* **12** 1252 (Aug. 12) 1933. Boger, A., and Voit, K. *ibid.* **12** 1642 (Oct. 21) 1933. Neumann, H. *ibid.* **12** 1444 (Sept. 16) 1933. Kemeny, E. *Orvosi hetil.* **76** 653 (Jul. 23) 1932. Hank, S. *ibid.* **77** 590 (July 8) 1933. Balazsy, D. *Deutsche med. Wchnschr.*

United States discussing the clinical value of prediction formulas. If such formulas are to be utilized extensively it is desirable to obtain the best one possible and to ascertain definitely its degree of accuracy. With this in mind the whole subject was reinvestigated.

In all the previous formulas the equation was obtained empirically by fitting a straight line to the data. Moreover, in each instance, the pulse rate and pulse pressure have been combined by addition. This is mathematically unsound, because pulse rate and pulse pressure cannot be expressed in the same units. Even though a line is obtained which seems to fit the data, it cannot be concluded that the equation of that line represents the true relationship between the variables studied.

In dealing with biologic data, several different types of curves can often be fitted to the observations with equally close agreement. In such cases another method of attack is more satisfactory. This method consists in the theoretical deduction of a definite type of equation. Each step in the process must be based on a fact or on a reasonable assumption. Then by the calculation of constants, an attempt is made to fit the data to the equation. By this method the discovery of a true biologic relationship can more reasonably be expected. This, therefore, is the method we have employed in reinvestigating the relationship between the consumption of oxygen and the pulse rate and pulse pressure.

#### DERIVATION OF THE FORMULA

The formula was derived by the following steps:

I. The total production of heat is proportional to the amount of oxygen consumed during the same period. This relationship is also assumed when metabolism is measured by indirect calorimetry and requires no further discussion.

II. The consumption of oxygen is proportional to the blood flow. This is a justifiable assumption because it has been shown that (1) the blood flow (minute volume) is increased in proportion to the oxygen consumed<sup>9</sup> and (2) the coefficient of utilization of oxygen is not changed in cases of thyrotoxicosis,<sup>10</sup> even when large volumes of oxygen are consumed.

<sup>59</sup> 1433, 1933. Olmes, H. *Arch d med, cir y especialid* **36** 645 (June 10) 1933. Schor, D. *România med* **11** 229, 1933. Balazsy, D. *Aerztli Nachrichten*, no. 16, 1933. Habs, H. *Munchen med Wchnschr* **80** 1260, 1933. Fine, A. *M J & Rec* **138** 221, 1933. Herzfeld, E., and Frieder, A. *Arch f Verdauungskr* **55** 199, 1934. Rachman, V. J. *Acta med Scandinav* **83** 95, 1934.

<sup>9</sup> Grollman, A. *The Cardiac Output of Man in Health and Disease*, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 234.

<sup>10</sup> Davies, H. W., Meakins, Jonathan, and Sands, J. *The Blood Gases and Circulation Rate in Hyperthyroidism*, *Heart* **11** 299, 1925.



The truth of equations (I) and (II) is supported by 102 observations on the blood flow in cases of thyroid disease. The term reference data will be used to distinguish these observations from our own. The data are from three reports, by (1) Davies, Meakins and Sands,<sup>10</sup> who worked in England and used the carbon dioxide-oxygen tension method of measuring blood flow, (2) Liljestrand and Stenstrom,<sup>11</sup> who worked in Sweden, and (3) Fullerton and Harrop,<sup>12</sup> in this country, both of whom used the method employing nitrous oxide.

By combining the first two steps the total production of heat is found to be proportional to the flow of blood. This is confirmed in

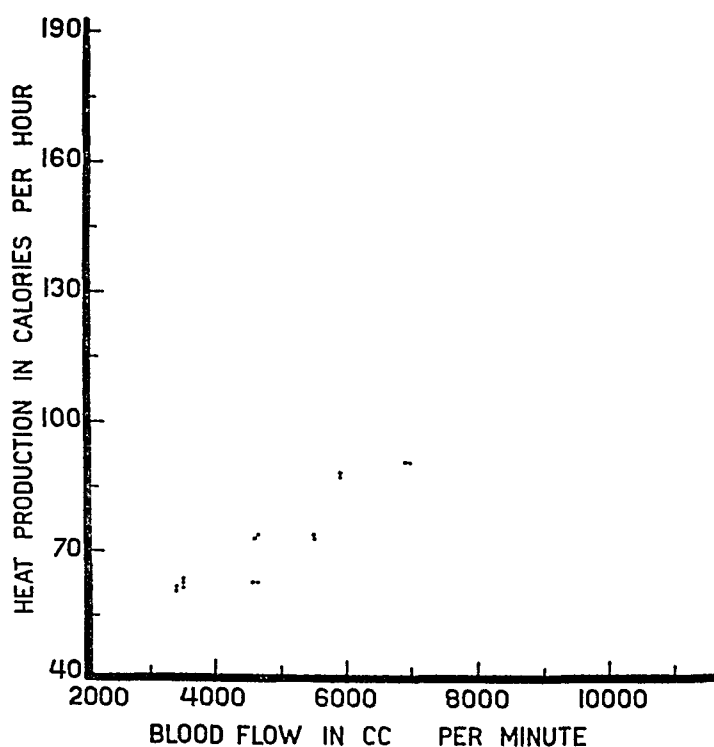


Chart 1—The relationship between the production of heat and the blood flow

chart 1, made from the reference data, which clearly indicates that the relationship holds over a wide range. The scatter may be entirely explained by the inaccuracies in the measurement of oxygen consumption and blood flow. The chart and the correlation coefficient, which is 0.9, suggest that a true proportionality exists between these variables.

III Blood flow is equal to pulse rate times stroke volume. The pulse rate can be determined easily, and the problem is to find a clinical

11 Liljestrand, G, and Stenstrom, N. Blood Flow and Blood Pressure in Exophthalmic Goiter, *Acta med Scandinav* 63 99, 1925.

12 Fullerton, C W, and Harrop, G A. Cardiac Output in Hyperthyroidism, *Bull Johns Hopkins Hosp* 46 203, 1930.

measure of the stroke volume. In a given individual, stroke volume is approximately proportional to pulse pressure. This does not hold in persons of various sizes, since a large heart pumps more blood per stroke at the same pulse pressure than does a small one. Some factor of size must therefore be introduced before stroke volume can be expressed in terms of pulse pressure. The surface area of the body seems to be the most satisfactory measure for this purpose. When this factor is introduced one has

IV Stroke volume is proportional to the pulse pressure times the surface area

The procedure thus far may be summarized in the following equations ( $K$  indicates a constant which has a different value in each equation)

$$(I) \text{ Total heat production} = K \times \text{oxygen consumed}$$

$$(II) \text{ Oxygen consumed} = K \times \text{blood flow}$$

Therefore, (IIa)  $\text{Total heat production} = K \times \text{blood flow}$

$$(III) \text{ Blood flow} = P R \times \text{stroke volume}$$

$$(IV) \text{ Stroke volume} = K \times P R \times S A$$

Therefore, (V)  $\text{Blood flow} = K \times P R \times P P \times S A$

Equation V is supported by chart 2, founded on the reference data. This chart indicates that equation V approximates the truth, although there is somewhat more scatter than in chart 1. Then, by the substitution of equation IIa in equation V the result is

$$(VI) \text{ Total heat production} = K \times P R \times P P \times S A$$

The final step in the derivation of the formula consists in dividing each side of equation VI by the surface area. This gives

$$(VII) \frac{\text{Heat production}}{\text{Surface area}} = K \times P R \times P P$$

$$\text{Or Calories per square meter per hour} = K \times P R \times P P$$

The use of the product of pulse rate and pulse pressure in the foregoing equations is further justified by the work of Murlin and Greer,<sup>13</sup> who concluded from their studies on the relation of heart action to the respiratory metabolism

Experiments on the human subject, in which respiratory metabolism and the heart action were determined simultaneously while the subject was resting and while doing a moderate amount of muscular work show that the product of pulse pressure (Erlanger<sup>14</sup>) by the pulse rate is a slightly better index of the oxygen absorption than the heart rate alone

13 Murlin, J. R., and Greer, J. R. The Relation of Heart Action to the Respiratory Metabolism, *Am J Physiol* **33** 253, 1914

14 Erlanger, J., and Hooker, D. R. An Experimental Study of Blood Pressure and Pulse Pressure in Man, *Johns Hopkins Hosp Rep* **12** 145, 1904

Variations in the blood flow caused by exercise, fever, ingestion of food, or anemia, which may not be accompanied by proportional changes in the consumption of oxygen, do not complicate the problem discussed here. Di-nitrophenol and its related compounds, which are known to increase metabolism without altering the pulse rate, should not complicate the problem, although their strange action calls for a solution. The only problem under consideration here is the relation of oxygen consumption to blood flow under strictly basal conditions, wherein the parallel deviations in oxygen consumption and blood flow usually result from disturbed thyroid or other endocrine function.

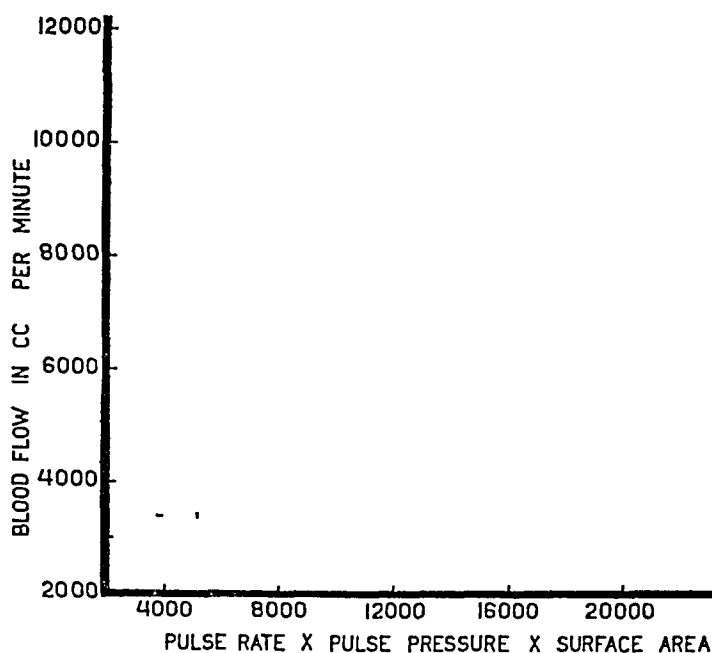


Chart 2—The relationship between the blood flow and the product of pulse rate, pulse pressure and surface area

#### THE DATA

After obtaining equation VII it was necessary to determine whether such an equation would be supported by actual observations. We proceeded to do this by gathering new data for the calculation of constants. These data (276 observations) were obtained in the departments of clinical calorimetry at the Stanford University Hospitals and St. Luke's Hospital, augmented by observations from private practice.

Extreme care was exercised in obtaining as accurate a measure of the blood pressure as possible. Several readings of the pressure were made while the patient was resting, either between the two test periods or at the end of the examination. The systolic pressure was determined

by auscultation and was checked by palpation and by observation of the changes in the amplitude of movement of the column of mercury. Auscultatory reading of the diastolic pressure was also checked by the motion of the mercury or the needle. Observations were continued until at least three successive checks were obtained. The pulse rate was recorded at frequent intervals during the test, and the lowest rates were averaged.

Since the large pulse pressure in cases of hypertension may not indicate an increased flow of blood, we considered it advisable to reject observations in which the diastolic pressure exceeded 90 mm of mercury. Because of the difficulty in obtaining accurate measurements, children under 15 years were omitted from the series. No other exclusions were made except of the occasional patient, usually with a cardiac irregularity, in whom an accurate measurement of the pulse rate or the blood pressure was impossible.

The product of the pulse rate and the pulse pressure was correlated with the number of calories per square meter per hour, and the constants of the equations were calculated in the usual way. Separate correlation tables were prepared for the two sexes, since women have, as a rule, a faster heart rate than men, yet the normal consumption of oxygen per unit of surface area of the former is less.

The formulas derived predict the number of calories per square meter per hour rather than the metabolic rate, as previous formulas have done. Any formula that gives the metabolic rate directly must do so by disregarding the normal standards. Since these vary from 33 calories per square meter per hour in old women to 46 calories in young men, a large error may thus be introduced. This error is of little importance in persons between the ages of 20 and 45, but it is considerable outside this range. There is no more reason for discarding the standards in a prediction formula than there is for doing so in the calculation of the basal metabolism by indirect calorimetry.

To our own observations we added those of the reference series and 104 reported from the Mayo Clinic,<sup>15</sup> which were suitable for this purpose. We augmented our data in order to obtain observations on patients with a very large and a very small consumption of oxygen and to eliminate the personal equation by including data of several observers. From these data the following formulas were derived:

For women    Calories per square meter per hour =  $0.0047 \times PP \times PR + 23$

For men        Calories per square meter per hour =  $0.0055 \times PP \times PR + 24$

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15 Sandiford, I. *Am J Physiol* **51** 407, 1920. Snell, A. M., Ford, F., and Rowntree, L. G. *Studies in Basal Metabolism*, *J A M A* **75** 515 (Aug 21) 1920. Boothby, W. M. *M Clin North America* **3** 603 (Nov) 1919. Bowen, B. D., and Boothby, W. M. *J Urol* **1** 469, 1917.

## ACCURACY OF PREDICTION FORMULAS

After the formulas were obtained the basal metabolic rate was calculated on each of our 276 cases, and the rate obtained was compared with that determined by indirect calorimetry. The disparity between the sets of values is shown in table 1. For comparison we show the results obtained with the formulas of Read,<sup>5</sup> the Gales<sup>6</sup> and Jenkins<sup>7</sup> on the same data. As a further test, we applied all four formulas to the reference data as well as to the observations from the Mayo clinic<sup>15</sup>.

A similar comparison of the accuracy of four prediction formulas<sup>16</sup> has been made by Rabinowitch,<sup>17</sup> who used 200 observations made in the Montreal General Hospital and 150 reported by Davies and Eason.<sup>18</sup> Examination of all the comparative studies shows that Jenkins'<sup>7</sup> formula gives good results when the rate is low but fails to predict the higher rates. The reverse is true for the Gales' formula.

Although the new formulas appear to possess greater prediction value over the entire range than any yet published, still one calculated rate of every three will differ by more than 10 per cent from the metabolism as determined by indirect calorimetry, and not infrequently even more misleading results are obtained. It is chiefly because of these occasional large discrepancies that the value of prediction formulas has been questioned.

However, before evaluating the results of the formulas, one must ascertain the greatest degree of accuracy which can be achieved. Presumably this should be perfect agreement with the metabolic rate in all cases. It is known, however, that the basal metabolism as determined by indirect calorimetry is not entirely accurate, and, unless it were, exact agreement could not be obtained. It is obviously impossible to obtain a degree of accuracy with any formula which surpasses the accuracy of the metabolism test itself. Consequently, one must first determine the reliability of clinical calorimetry as it is performed as a routine procedure.

The question of the reliability of indirect calorimetry first arose when this clinical method was introduced as a substitute for the complicated procedure of direct calorimetry. The latter has an error of from 0.5 to 1.2 per cent<sup>19</sup> in its measurement of the production of

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16 Read, J. M., and Barnett, C. W. New Formulae for Prediction of Basal Metabolism from Pulse Rates and Pulse Pressure, *Proc Soc Exper Biol & Med* **31** 723, 1934. Read<sup>4, 5</sup> Jenkins<sup>7</sup>

17 Rabinowitch, I. M. Prediction of Basal Metabolism from Pulse Pressure and Pulse Rate, *Canad M A J* **32** 135 (Feb) 1935.

18 Davies, H. W., and Eason, J. The Relation Between the Basal Metabolic Rate and the Pulse Pressure in Conditions of Disturbed Thyroid Function, *Quart J Med* **18** 36, 1924.

19 Sonderstrom, G. F., Meyer, A. L., and DuBois, E. F. Clinical Calorimetry XI, *Arch Int Med* **17** 872 (June) 1916.

TABLE 1—*Accuracy of Various Prediction Formulas Compared with That of Determinations by Indirect Colorimetry \**

Data		Error Less Than												Error Over 25%																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
Source	No of Observations	B M R Range, Percentage	5%			10%			15%			20%			25%			R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J

\* The comparative prediction values of four formulas are shown R stands for Read (1924), G for Gale, J for Jenkins, and R B for the new formulas presented in this paper The average deviation was as follows Read, 9.3 per cent, Gale, 10.3 per cent, Jenkins, 10 per cent, and Read Barnett, 8.2 per cent

heat, the magnitude of error decreasing as the test period is lengthened Gephart and DuBois,<sup>20</sup> in a series of thirty periods of one hour each, with a normal subject, noted that the results of the two methods agreed within 5 per cent in 70 per cent and within 10 per cent in 90 per cent of the periods. This careful comparison of direct with indirect calorimetry by experienced workers, however, furnishes no measure of the average error of basal metabolism as it is ordinarily determined.

In nearly every laboratory for the study of metabolism two observation periods are recorded for each patient. The agreement between the tracings made for the same patient should gauge the accuracy of the method and from a large number of tracings a close estimate of the distribution of errors in the determination of metabolism can be obtained. We accordingly collected 530 records from five different laboratories. Each was a record of at least two and sometimes three, separate periods of observation. The metabolic rates were calculated from the curves, and the agreement between the high and the low values on each tracing were noted. When the disagreement is large it is a widespread practice to consider the test unsatisfactory and to discard it. All such tests must, however, be included if one is to give a true idea of the reliability of the method. In a laboratory where unsatisfactory tracings are discarded a closer agreement than we are reporting would obviously be obtained on reviewing the records, but this would indicate a greater accuracy in indirect calorimetry than really exists.

The error in estimating basal metabolism has been studied by Wishart<sup>21</sup> and Jenkins.<sup>22</sup> The latter reported that the mean difference between the lower and the higher of two rates taken in succession during the same period was 4.7 per cent in over 4,000 tests. The mean difference obtained by us in 530 tests was 7.5 per cent. In table 2, the disparity between the pairs of observations on the basal metabolic rate is given. Since this is a measure of the accuracy of clinical calorimetry, it is impossible to obtain a greater degree of accuracy with any formula. For comparison we indicate the agreement between the rate calculated by our formulas and the rate determined in the laboratory. In each column the accuracy of prediction of the formulas is only slightly less than the accuracy of the test of the metabolic rate itself. Consequently we believe that the formulas give results that are almost as good as can be obtained until a more satisfactory method of determining the metabolic rate is available.

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20 Gephart, F. C., and DuBois, E. F. Clinical Calorimetry. IV. Arch. Int. Med. **15** 835 (June) 1915.

21 Wishart, G. M. The Variability of Basal Metabolism, Quart. J. Med. **20** 193, 1927.

22 Jenkins, R. L. The Error of Basal Metabolism Determination and the Normal Range of Basal Metabolism, Arch. Int. Med. **49** 181 (Feb.) 1932.

It should be stated that the larger deviations between the calculated and the measured rate were in the very low and very high ranges, where the actual figure is less important. It makes little difference in an obviously thyrotoxic patient whether the basal metabolic rate is plus 55 or 65 per cent. Determinations of the metabolic rate are most often resorted to in order to ascertain whether the rate is normal or abnormal. For this purpose, prediction formulas are valuable, as they seldom show an abnormal rate in a normal person.

TABLE 2—*Comparison of Basal Metabolic Rate by Formula and by Indirect Calorimetry*

	No of Observations	Error Less Than					Error Over 25%
		5%	10%	15%	20%	25%	
Comparison of tracings by indirect calorimetry	530	49	77	90	96	97	3
Agreement between BMR by formula and by calorimetry	276	45	73	88	93	98	2

TABLE 3\*—*Standards for Prediction of the Metabolic Rate According to the Authors' Formulas*

Basal Metabolic Rate	Men	Women
From 14 to 16 years	$0.012 \times P R \times P P - 48$	$0.011 \times P R \times P P - 46$
From 16 to 18 years	$0.013 \times P R \times P P - 44$	$0.012 \times P R \times P P - 42$
From 18 to 20 years	$0.013 \times P R \times P P - 41$	$0.012 \times P R \times P P - 39$
From 20 to 30 years	$0.014 \times P R \times P P - 39$	$0.013 \times P R \times P P - 38$
From 30 to 40 years	$0.011 \times P R \times P P - 39$	$0.013 \times P R \times P P - 37$
From 40 to 50 years	$0.014 \times P R \times P P - 38$	$0.013 \times P R \times P P - 36$
From 50 to 60 years	$0.015 \times P R \times P P - 36$	$0.013 \times P R \times P P - 34$
From 60 to 70 years	$0.015 \times P R \times P P - 34$	$0.014 \times P R \times P P - 32$
From 70 to 80 years	$0.016 \times P R \times P P - 32$	$0.014 \times P R \times P P - 30$

\* The data for this table are calculated on the Sage normal standards (DuBois, E. Basal Metabolism in Health and Disease, Philadelphia, 1927, p. 200). The standards differ slightly, but not significantly from those of Boothby and Sandiford (Am J Physiol 90: 291, 1929).

If it is desired to employ the prediction formulas to calculate the basal metabolic rate directly without reference to the normal standards, table 3 may be used. It is derived from the formulas presented here and takes cognizance both of age and of sex.

#### SUMMARY

A new method for the derivation of formulas for predicting the basal metabolic rate from pulse rate and pulse pressure is reported.

The accuracy of the new formulas is compared with that of certain former ones.

The inaccuracy of the determination of basal metabolism by indirect calorimetry is pointed out.



The accuracy of the new formulas is shown to compare favorably with the accuracy of clinical calorimetry

#### CONCLUSIONS

These formulas are valuable for (1) estimating the basal metabolic rate if the facilities for measuring the consumption of oxygen are not available and (2) checking the reliability of the metabolic rate as determined by indirect calorimetry. If there is a marked disparity between the results obtained by the two methods the test should be repeated. In many cases the metabolic rate predicted by the pulse rate and pulse pressure obtained in the morning before the patient arises may be more accurate than the rate determined by measuring the consumption of oxygen after the patient has arisen, dressed and traveled to a laboratory.

# CHANGES IN TEMPERATURE OF THE SKIN FOLLOWING THE INGESTION OF FOOD

GEORGE BOOTH, M D

AND

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The weight of a person is dependent on the balance of the intake and the output of energy. There is, however, no information which explains why some persons are contented with an intake equal to their energy output while others choose an excessive or a deficient intake of food. It is possible that the sensation of satiety is the controlling factor in making this choice. The physiologic reactions which are the components of this sensation have not been fully established. The production of heat resulting from the ingestion of food is well known, and it is conceivable that the sudden change in the rate of production of heat by the body during a meal may bear some relation to the sensation of satiety. The disposition of the heat, particularly its dissipation, may be of importance in this relationship. One factor of the dissipation of heat is reflected in the changes in the temperature of the skin. This report describes observations on skin temperature and blood pressure following a meal of meat which was designed to attain satiety.

No previous studies bearing on this point have been noted in the literature. Talbot<sup>1</sup> and McClure and Sauer<sup>2</sup> reported observations on the temperature of the skin of infants which extended over a feeding period. They observed no change in the temperature in response to the food. No descriptions of the meals were given, and it is assumed that they were ordinary feedings not particularly designed to cause satiety. Keller<sup>3</sup> reported a single observation of a rise of 3 C in the arm following a meal. Here, again, the meal was not described.

## METHOD

The meal used was designed to attain satiety as quickly as possible and to yield a maximum production of heat. Ground beefsteak, with sufficient stewed

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From the Medical Service of the Western Pennsylvania Hospital

1 Talbot, F B. Skin Temperatures of Children, *Am J Dis Child* **42** 965 (Oct) 1931

2 McClure, W B, and Sauer, L W. The Influence of Clothing on the Surface Temperature of Infants, *Am J Dis Child* **10** 425 (Dec) 1915

3 Keller, C, quoted by Cobet, R. Die Hauttemperatur des Menschen, *Ergebn d Physiol* **25** 439, 1926

tomatoes to render it palatable, was the meal chosen. The subjects were requested to eat as much as they could possibly consume, using as much time as they desired to do so.

The temperature of the skin was determined with a Tycos dermotharm<sup>4</sup> at the palm of the hand and the ball of the thumb and at the sole of the foot and the ball of the great toe. These points were chosen because in our preliminary observations of fifteen of the points described by Benedict<sup>5</sup> these four points showed the maximum variations in temperature. At the start of a test period, preliminary readings were taken until the temperature became stabilized at each point. This usually required from ten to twenty minutes after the acclimatization of the subject. For each observation readings were then taken at each point until constant within 0.1 C., usually from two to four readings. The average of the readings was taken for each point, and the average of the four points was taken for each time interval. The cycle of observations was repeated at two minute intervals for approximately one hour. It was impossible to continue the observations for a longer period because of the appearance of restlessness on the part of the subjects as well as fatigue on the part of the observers.

The readings for blood pressure were taken with a mercury manometer by the auscultatory method. Readings were taken at two minute intervals throughout the period of observation.

Environmental conditions were kept constant within prescribed limits. With few exceptions the room temperature throughout each experiment was kept constant within 1 C., the average variation being 0.7 C., at a level which was comfortable for the individual subject. The room temperatures selected ranged from 20 to 25 C. Wet and dry bulb thermometer readings were recorded in most instances, and, as has been observed by others, the humidity within normal limits, exerted no detectable influence on the temperature of the skin. An electric fan running at a constant speed was placed in a distant part of the room in order to insure a uniform circulation of air. The subject was protected from currents of wind by a series of screens. He was seated in a comfortable chair with the legs resting on a stool, so that the feet were on a level with the seat of the chair. Both arms and both legs were exposed equally throughout the preliminary period and the test period. All tests were done at 4 o'clock in the afternoon, and the subject had fasted since breakfast on the day of the test.

The subjective and objective symptoms experienced by the subjects were recorded at the time of their appearance. Those encountered were a feeling of warmth, the appearance of gross perspiration, a feeling of drowsiness, sleep and finally restlessness.

Twenty-one observations were made on persons of normal weight. The subjects were all within a range of from 90 to 110 per cent of their theoretically ideal weight and were free from any detectable disease.

Seventeen observations were made on persons who weighed more than 110 per cent of their theoretically ideal weight, the minimum being 111 per cent, the maximum 194 and the average 149.

Two types of control observations were carried out. Five of the persons of normal weight and three of the obese subjects were observed under the standard conditions of the test except that the meal was omitted. The effects of

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<sup>4</sup> The observations were made with a Tycos dermotharm, which was supplied by the Taylor Instrument Company, Rochester, N. Y.

<sup>5</sup> Benedict, F. G. *Measurement of the Skin Temperature of Humans*, Leopoldina, no. 4, 1929, p. 129.

variation in room temperature, insufficient acclimatization of the subjects and fatigue were observed in two of the subjects. The base line curve was obtained from the other six.

Three of the subjects of normal weight were observed while eating a meal of meat which did not attain the level of satiety.

With these standards established, certain of the experimental and control observations were discarded. Two of the experimental and one of the control observations were discarded because of sudden variations in room temperature which seemed to have a direct effect on the temperature of the skin. One control observation was discarded because the acclimatization of the subject was not complete. A single point, the great toe, was unusually cold at the onset, and suddenly warmed, some time after the temperature had apparently reached a stable level, causing a rise of 2.5 C in the average curve. Another control observation was discarded because of subjective cooling during the period of observation, accompanied by a sharp fall in the temperature of the skin. One subject of the experimental series was found to have a blood pressure of 190 systolic and 110 diastolic. This record was omitted in order to avoid the possibility of a complicating factor in the vascular disease. Another subject in the experimental series experienced a violent emotional storm in her endeavor to outstrip one of her fellow patients in eating ability. The systolic blood pressure rose 50 mm, and the temperature of the skin rose 1.6 C in two minutes. This record was omitted. There was one "sport" in the entire group. The deviation of the temperature of the skin from the mean was greater than four times the average deviation from the mean. This record was omitted.<sup>6</sup>

For purposes of analysis the data obtained were charted in graphs, with the numbers of grams of meat eaten, the systolic and diastolic blood pressure in millimeters of mercury and the temperature of the skin to 0.1 C as ordinates, and the time intervals, two minutes, as abscissas. Such graphs were constructed for each individual experiment. Composite graphs were then made of the reactions of the normal, the obese and the control groups. On the graphs certain particular time intervals were marked off, namely, the start of the meal, the completion of the meal and the point of maximum variation of the temperature of the skin. The appearance of subjective or objective symptoms was also noted.

#### OBSERVATIONS

*Subjects of Normal Weight*—Nineteen acceptable observations were made on seventeen persons of normal weight. The average amount of meat eaten was 505 Gm, the maximum was 900 Gm and the minimum was 150 Gm. Only five of the nineteen subjects ate less than 400 Gm. The average time of eating was twenty-two minutes, the maximum was thirty-six minutes and the minimum was twelve minutes.

A composite curve of the temperature reactions of the skin of the group showed a rise shortly after the start of the meal and a steady rapid increase for forty minutes. This was followed by a further slight increase to the maximum elevation in sixty minutes (chart 1). The earliest onset of the reaction was four minutes, the latest thirty-six minutes and the average ten minutes. The minimum elevation was +0.9 C, the maximum +4.7 C and the average 2 C. Sixteen of the nineteen exhibited reactions which corresponded to the average pattern of the curve.

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<sup>6</sup> Goodwin, H. M. *Precision of Measurements and Graphical Methods*, New York, McGraw-Hill Book Company, 1913, p. 21.

The composite curve of the blood pressure showed a rise of 10 mm of mercury, both systolic and diastolic, at the start of the meal and a return to normal at its completion. This reaction was uniform throughout the series.

In three subjects in the series the experiment was repeated after an interval of two years, and the results in two instances were remarkably similar. The meat eaten by one subject (table 1, case 1) amounted to 500 Gm and 650 Gm, respectively, the initial rise in temperature of the skin occurred in ten minutes

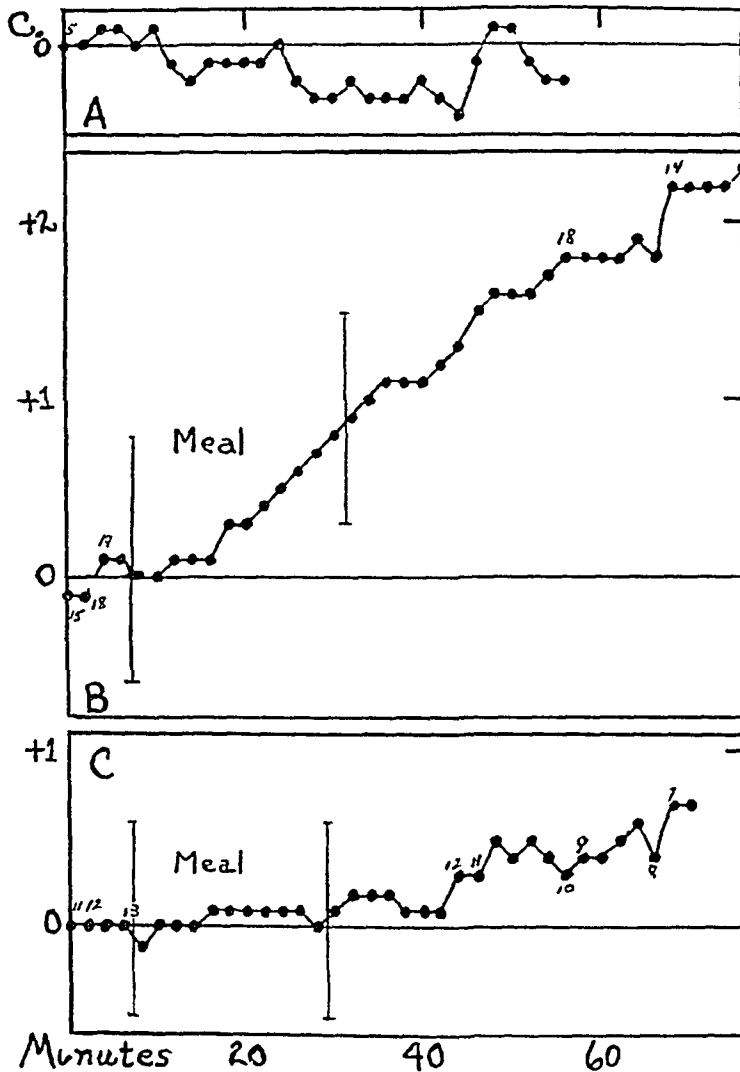


Chart 1—Composite curves of the temperature reactions of the skin during the control period with the meal omitted (*A*) and of persons of normal weight (*B*) and obese persons (*C*) before, during and after a meal of meat to the level of satiety

and twelve minutes, and in each experiment the maximum elevation was  $+2.6^{\circ}\text{C}$ . The meat eaten by another (table 1, case 2) amounted to 600 Gm in each experiment, the initial reaction occurred in eighteen and twelve minutes, respectively, and the maximum elevations were  $+4.1^{\circ}\text{C}$  and  $+4.6^{\circ}\text{C}$ . The reaction of the third subject differed only in intensity (table 1, case 3). The meal eaten amounted

to 700 Gm in both tests, the initial rise in the temperature of the skin occurred in thirty-four and six minutes, respectively, and the maximum elevations of temperature were  $+0.7^{\circ}\text{C}$  and  $+1.9^{\circ}\text{C}$ .

*Obese Subjects*—Fourteen acceptable observations were made on eleven obese persons. The average amount of meat eaten was 490 Gm, the maximum was 1,050 Gm and the minimum was 150 Gm. Four of the thirteen subjects ate less than 400 Gm. The average time of eating was twenty minutes, the maximum thirty-six minutes and the minimum fourteen minutes.

A composite curve of the temperature reactions of the skin showed a rise beginning a considerable time after the start of the meal and a relatively small maximum elevation (chart 1). The most rapid onset of the reaction was after four minutes, and the most delayed onset was after forty-six minutes. The average was twenty-four minutes. The maximum elevation was  $+3.7^{\circ}\text{C}$ , the maximum drop in temperature was  $-2.1^{\circ}\text{C}$ , and the average change was only  $+0.6^{\circ}\text{C}$ ,

TABLE 1—*Original Observations and Those Made Several Years Later*

Case	Date	Percentage of Ideal Weight	Surface Area, Sq M	Meat Meal, Gm	Time of Initial Change in Skin Tem- perature, Minutes	Maximum Change in Skin Tem- perature, $^{\circ}\text{C}$	Time of Maximum Change in Skin Tem- perature, Minutes
1	11/13/31	102.6	1.85	500	10	$+2.6$	44
	11/19/33	100.0	1.84	650	12	$+2.6$	38
2	11/18/31	96.6	1.75	600	18	$+4.1$	64
	11/19/33	98.0	1.76	600	12	$+4.6$	82
3	11/17/31	94.0	1.82	700	34	$+0.7$	54
	11/20/33	94.0	1.82	700	6	$+1.9$	38
4	11/24/31	171.7	2.04	400	2	$-0.5$	30
	11/27/33	178.6	2.09	550	28	$-1.0$	44
5	12/ 1/33	150.5	1.95	750	4	$+3.6$	46
	1/16/34	131.4	1.85	600	8	$+1.1$	72
6	12/ 1/31	110.7	1.72	750	46	$-1.0$	64
	12/13/33	104.9	1.67	900	4	$+4.2$	64
7	11/11/31	116.8	2.11	500	8	$+0.5$	22
	12/ 3/33	108.8	2.05	900	14	$+1.3$	50

in contrast with  $2^{\circ}\text{C}$  in the group of normal weight. Six of the fourteen failed to show the characteristic pattern of curve.

A composite curve of the blood pressure in this group showed a prompt rise of 10 mm of mercury, both systolic and diastolic, and a return to the previous level at the completion of the meal. There was no difference in the response of the blood pressure in the two groups.

The experiment was repeated with four subjects in this series, and in three instances the resulting curves were similar in contour to the first one (table 1). The meat eaten by one subject (case 4, table 1) amounted to 400 Gm and, two years later, 550 Gm. The initial rise occurred in two and twenty-eight minutes, respectively, and the maximum variation in temperature was  $-0.5^{\circ}\text{C}$  and  $-1^{\circ}\text{C}$ . The meat eaten by the second subject (table 1, case 5) amounted to 750 Gm and, one month later, 600 Gm. The initial reaction occurred in four and eight minutes, respectively, and the maximum change was  $+3.6^{\circ}\text{C}$  and  $+1.1^{\circ}\text{C}$ . The third subject (table 1, case 7) ate 500 Gm of meat at the first test and 900 Gm two years later at the second test. The initial changes in the temperature of the skin occurred in eight and fourteen minutes, respectively, and the maximum changes

were  $+0.5^{\circ}\text{C}$  and  $+1.3^{\circ}\text{C}$ . There was a change in the reaction on the second test of the fourth subject (table 1, case 6). The subject first ate 750 Gm of meat and two years later 900 Gm. The initial changes in the temperature of the skin occurred in forty-six and four minutes, respectively, and the maximum changes were  $-1^{\circ}\text{C}$  and  $+4.2^{\circ}\text{C}$ .

*Control Group*—Acceptable observations were made on two persons of normal weight and three obese persons with the meal omitted (chart 1). A composite curve of the temperature reactions of the skin of the control group showed a fall of  $0.2^{\circ}\text{C}$  in fifty-six minutes. The maximum elevation was  $+0.9^{\circ}\text{C}$ , and the maximum drop was  $-1.2^{\circ}\text{C}$ . The reaction followed the same pattern in both the persons of normal weight and the obese subjects.

The blood pressure showed no variation throughout the observation period.

Three persons of normal weight, who had previously served as subjects for the experiments on satiety and had exhibited reactions which followed the normal pattern of the curve, were observed during a meal of meat which did not attain the level of satiety. In each instance the temperature reaction of the skin was decidedly less intense than the reaction to the satiety meal. The data obtained are included in table 2.

TABLE 2—*Observations on Three Persons While Eating a Meal of Meat Below the Level of Satiety*

Meat, Gm	Time of Initial Change in Skin Temperature, Minutes	Maximum Change in Skin Temperature, $^{\circ}\text{C}$	Time of Maximum Change in Skin Temperature, Minutes
200	10	$-1.8$	44
400	16	$+0.5$	26
450	16	$+0.8$	30

In the control experiments the blood pressure showed a prompt rise of 10 mm of mercury, systolic and diastolic, and a return to the previous level at the completion of the meal.

#### COMMENT

*Blood Pressure*—In all experiments, in the persons of normal weight as well as in the obese subjects, the blood pressure reaction was uniform. There was a rise in blood pressure immediately following the start of the meal and a return to the previous level immediately following the completion of the meal. The reaction seemed to be related to the exertion of eating rather than to the characteristics of the subjects or of the meals.

*Meal*—It may be noted that the average meal eaten by the group of normal weight appears to have been slightly larger than that of the obese group. This difference is due to the uneven distribution of the sexes in the two groups. The men in both groups consumed an average of 619 Gm of meat, whereas the women averaged only 420 Gm. This sex difference was characteristic of both the obese group and the group of normal weight, as will be described later. The obese group was

composed of four men and ten women, whereas there were nine men and ten women in the group of normal weight, which precludes a direct comparison of the unweighted average figures for intake of food of the two groups

*Skin Temperature*—It should be emphasized that our interest was in the variation in the temperature of the skin over a short period rather than in the actual level of the temperature. With the precautions observed, we think that the reactions are sufficiently uniform to justify consideration. Additional evidence of the uniformity of the reaction is offered by the repetition of the observations on seven of the subjects (table 1). For four of the seven the contour of the curves corresponded closely. At the time of the original observations on two of the remaining subjects they were classified as mildly obese, and the temperature reactions of the skin corresponded to those exhibited by the obese group. Before the second observations were made they had reduced to 105 and 109 per cent of their theoretical ideal weight. At this time both reactions corresponded to the normal. In one instance there was a change in the character of the reaction without any change in weight (table 1, case 3). No explanation of this reaction is offered.

The two points of particular interest in a comparison of the reactions of the persons of normal weight and those of the obese group are the difference in the magnitude of the elevation of skin temperature and the difference in the time of its occurrence. In regard to magnitude, an isolated observation of a difference of 1.4 C might not be remarkable. However, a difference of 1.4 C between the average figures of eighty readings for each time interval for the group of normal weight and those of fifty-two readings for each time interval for the obese group is significant. The time of the reaction in relation to the meal is perhaps of more significance. The initial reaction was observed in ten minutes in the group of normal weight, in contrast to twenty-four minutes in the obese group. The time relationship is illustrated in chart 2, which shows composite curves of the observations during the control period, during the meal and after the completion of the meal, in separate phases.

In the group of normal weight, ten minutes after the beginning of the meal there was a rise in the temperature of the skin which continued and amounted to 0.9 C in twenty-two minutes when eating stopped. There was a further steady increase to 1.8 C in forty minutes. The maximum elevation of 2 C was attained in the third twenty minute period.

In the obese group the elevation of the temperature of the skin at the time of cessation of eating, twenty minutes after the meal was begun, was only 0.1 C. After the period of eating there was a further rise to the maximum of 0.5 C in forty minutes. This level was main-



tained without essential change during the next twenty minutes of observation. The elevation of only 0.1 C during the period of eating in this group is in marked contrast to the elevation of 0.9 C in the group of normal weight.

*Surface Area*—In view of the relationship between the surface area and the metabolism of a subject, that property might be expected to be a factor of influence in the phenomenon reported here. The average surface area of the group of normal weight was 1.67 square meters  $\pm 0.15$  (table 3). In the obese group the average area was 2.01 square meters  $\pm 0.11$ . If the two groups are each subdivided into one group with reactions which followed the average pattern and another group with reactions which followed the average pattern and another group

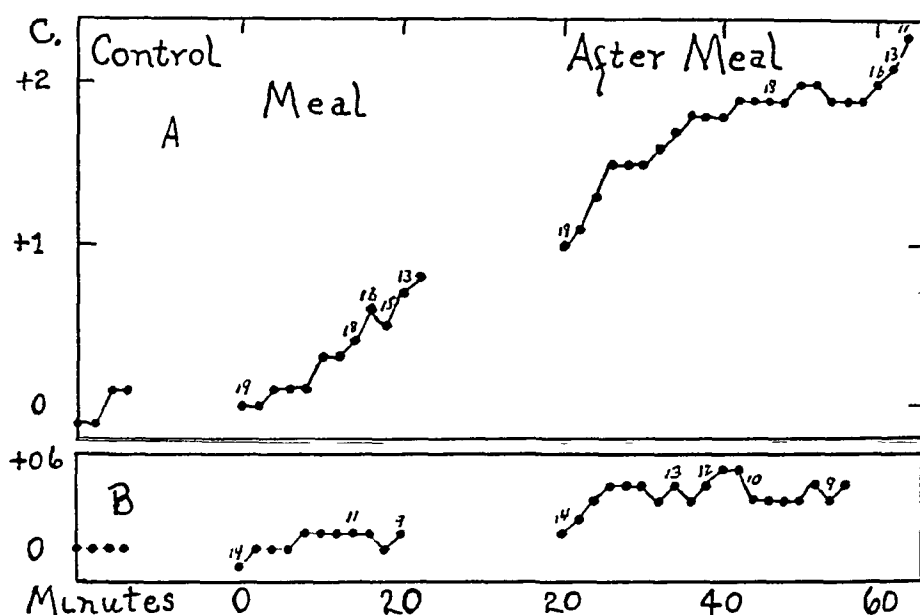


Chart 2—Composite curves showing the relation of the magnitude of the elevation of the temperature of the skin and the time of its occurrence in persons of normal weight (A) and obese persons (B) during the control period and during and after the meal.

with reactions which failed to follow the average pattern, the exact importance of the factor of surface area may be more clearly defined. In the group of normal weight the reactions of sixteen subjects followed the average pattern, and the average surface area was 1.69 square meters  $\pm 0.15$ . The average area of the four whose reactions failed to follow the average pattern was 1.58 square meters  $\pm 0.16$  (table 3).

In the obese group the average surface area of the seven subjects whose reactions followed the average pattern was 2.08 square meters  $\pm 0.10$ . The average area of the remainder of the group was 1.94 square meters  $\pm 0.13$ .

The individual curves did not bear any relationship to the corresponding individual surface areas. Some of the higher elevations of skin temperature occurred in subjects with large surface area, and some of the more pronounced instances of lowering of the temperature occurred in persons with a small surface area in both the subjects of normal weight and the obese group. For example, in the group of normal weight the two subjects with the largest surface area, 1.9 and 1.85 square meters, each had an elevation of temperature of  $+2.6^{\circ}\text{C}$ , whereas the two subjects with the smallest surface area, 1.36 and 1.39 square meters, had elevations of  $+1.8^{\circ}\text{C}$  and  $+1.4^{\circ}\text{C}$ . In the obese group the two subjects with the largest surface area, 2.4 and 2.14 square meters, had elevations of temperature of  $+0.7^{\circ}\text{C}$  and  $+3.6^{\circ}\text{C}$ , whereas the two subjects with the smallest surface area, 1.7 and 1.81 square meters, had elevations of temperature of  $+1.8^{\circ}\text{C}$  and  $-1.2^{\circ}\text{C}$ . It

TABLE 3—*The Surface Area in Relation to Changes of Temperature of the Skin*

	Subjects	Surface Area, Sq. M.	Average Deviation from Mean
Normal group	19	1.67	$\pm 0.15$
Obese group	14	2.01	$\pm 0.11$
Normal group with normal reaction	15	1.69	$\pm 0.15$
Normal group with no elevation of skin temperature	4	1.58	$\pm 0.16$
Obese group with obese reaction	8	2.08	$\pm 0.10$
Obese group with elevation of skin temperature	6	1.94	$\pm 0.13$

appears, therefore, that the surface area is not the controlling factor in the reaction.

*Sex Difference*—On analysis for other possible factors of influence, it was observed that there was a slight but consistent difference in the magnitude of the reaction in the two sexes (chart 3). In the group of normal weight the meals taken by the ten women averaged 365 Gm of meat, with a minimum intake of 150 Gm and a maximum of 900 Gm. The nine men in the group of normal weight took an average of 633 Gm of meat, with a minimum of 500 Gm and a maximum of 900 Gm. The average elevation of the temperature of the skin of the women was  $+1.6^{\circ}\text{C}$ , the minimum  $+1.1^{\circ}\text{C}$  and the maximum  $+4.6^{\circ}\text{C}$ . The average elevation of the temperature of the skin of the men was  $+2.1^{\circ}\text{C}$ , the minimum  $+0.9^{\circ}\text{C}$  and the maximum  $+4.7^{\circ}\text{C}$ .

In the obese group, ten women ate an average of 475 Gm of meat. The minimum was 150 Gm, and the maximum was 750 Gm. In the same group, the four men ate an average of 588 Gm of meat. The minimum was 300 Gm, and the maximum was 1,050 Gm. The elevation

of temperature among the women was average  $+0.4^{\circ}\text{C}$ , minimum  $-2.1^{\circ}\text{C}$  and maximum  $+3.7^{\circ}\text{C}$ . In the group of obese men the average elevation of temperature was  $+1.2^{\circ}\text{C}$ , the minimum  $+0.3^{\circ}\text{C}$  and the maximum  $+2.4^{\circ}\text{C}$ .

A comparison of the meals eaten by the two groups brings out the fact that the ten obese women ate a considerably larger meal than the ten women of normal weight. In the case of the men the average of nine persons of normal weight was slightly higher than that of the

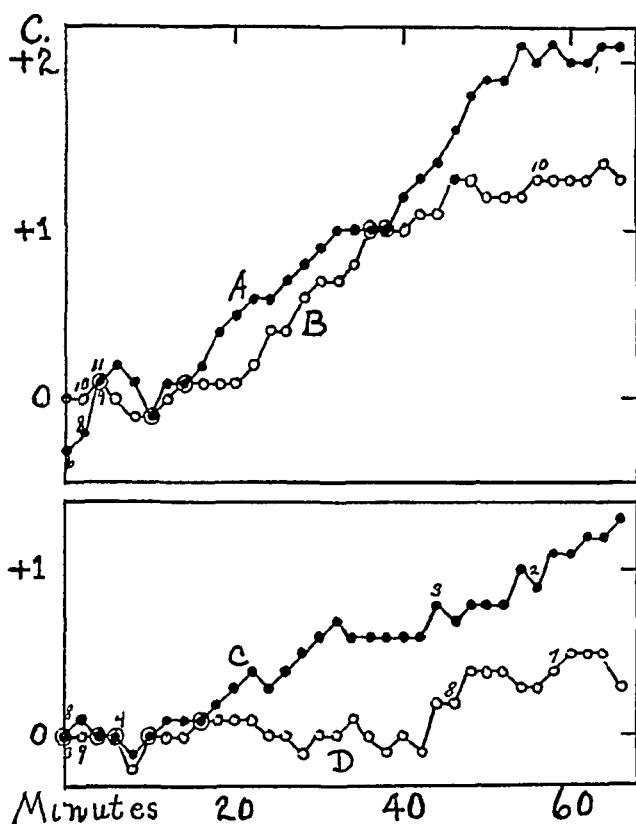


Chart 3—Composite curves showing the difference in the magnitude of the temperature reaction of the skin between the sexes. *A* is the curve for men of normal weight, *B*, for women of normal weight, *C*, for obese men, and *D*, for obese women.

obese men, but there were only four of the latter, not a large enough group to offer comparable figures.

*Relation of Changes in Temperature of the Skin to Satiety*—In these experiments the attainment of satiety, as evidenced by the cessation of eating, was also marked by a sensation of warmth in most cases and by the appearance of gross perspiration in some. These phenomena emphasize the importance of the production and dissipation of heat in the response of the body to the ingestion of food. In studies of the

specific dynamic action of food, Strang and McClugage<sup>7</sup> emphasized the physiologic load thrown on the body in normal persons by the rapid change in the production of heat resulting from the ingestion of food. One aspect of the physiologic dissipation of the extra heat is described by the observations on the temperature of the skin. The rapid change in temperature is probably responsible for the sensation of warmth usually experienced, as it has been demonstrated by Bazett<sup>8</sup> that this sensation is the result of the rate of change of the temperature of the tissues surrounding the nerve end-organs in the skin rather than the result of changes in the actual temperature of the tissues. Accordingly, it is conceivable that the intensity of the sensation of warmth may be one important component of the sensation of satiety. Certainly in persons of normal weight the inability to continue eating coincided with a rise of 0.9 C. in only twenty-two minutes.

In obese subjects the total production of heat in response to food is probably the same as in persons of normal weight. Although the total production of heat is the same, studies of the specific dynamic action<sup>7</sup> showed a slower rate of change of the rate of production of heat and, furthermore, the maximum point of the rate of change was definitely delayed. This phenomenon is conceivably reflected in the diminished and delayed elevation of the temperature of the skin in the obese subjects reported on here. The resulting decrease in the intensity of the sensation of warmth may be one factor in the delay of the sensation of satiety, permitting the consumption of food in excess of the actual physiologic requirement.

#### CONCLUSIONS

Observations on the blood pressure and the temperature of the skin after a meal of meat designed to attain satiety were made on nineteen persons of normal weight and fourteen obese subjects.

The response of the blood pressure was identical in the two groups and probably due solely to the work of eating.

In the group of normal weight there was an elevation of the temperature of the skin, which began shortly after the start of the meal and reached a maximum of 2 C. in sixty minutes.

The elevation of the skin temperature in the obese group was definitely diminished and delayed as compared with that of the group of normal weight.

It is suggested that the difference in reaction may be one factor in the delayed sensation of satiety in obese persons and therefore a controlling factor in the determination of the large intake of obese persons.

7 Strang, J. M., and McClugage, H. B. The Specific Dynamic Action of Food in Abnormal States of Nutrition, *Am J M Sc* **182** 49, 1931.

8 Bazett, H. C. Physiological Responses to Heat, *Physiol Rev* **7** 531, 1927.

# CLINICAL VALUE OF THE TEST FOR HIPPURIC ACID IN CASES OF DISEASE OF THE LIVER

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A satisfactory test of the function of the liver should (1) detect and estimate hepatic insufficiency, (2) aid in a differential diagnosis, (3) have prognostic usefulness and (4) contribute toward a better understanding of the physiology of the liver. With these objectives, the synthesis of hippuric acid (benzoic acid + amino-acetic acid = hippuric acid) was studied both experimentally and clinically<sup>1</sup>. It was observed that the hourly rate of excretion of hippuric acid in normal persons following the ingestion of sodium benzoate is remarkably constant, being influenced only somewhat by the size of the subject or, more exactly, by the surface area. In certain types of disease of the liver, however, the output of hippuric acid is markedly reduced. This reduction is due primarily to the diminished capacity of the liver to synthesize amino-acetic acid and in part to damage of the enzymatic mechanism which unites benzoic acid with amino-acetic acid. In man, as in the rabbit, this conjugating enzyme is present mainly in the liver, and the small amount which occurs in the kidneys is insufficient to compensate when injury to the liver occurs. The output of hippuric acid after the ingestion of benzoic acid can therefore be considered a measure of the liver's capacity to furnish amino-acetic acid and also an index of its detoxifying power. Fortunately, the adaptation of this test for clinical use presents no difficulties, since both the procedure for carrying out the test on the patient and that for determining the amount of hippuric acid in the urine are simple and require no elaborate equipment. Since the first report the test has been applied in a larger

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Part of the paper was read before the New York Academy of Medicine, Section of Medicine, March 20, 1934

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1 Quick, A. J. The Study of Benzoic Acid Conjugation in the Dog with a Direct Quantitative Method for Hippuric Acid, *J. Biol. Chem.* **67** 477 (Feb) 1926, The Conjugation of Benzoic Acid in Man, *ibid.* **92** 65 (June) 1931, On the Chemistry of the Conjugation of Benzoic Acid, *ibid.* **95** 189 (Feb) 1932, The Site of the Synthesis of Hippuric Acid and Phenylacetic Acid in the Dog, *ibid.* **96** 73 (April) 1932. Quick, A. J., and Cooper, M. A. The Effect of Liver Injury on the Conjugation of Benzoic Acid in the Dog, *ibid.* **99** 119 (Dec) 1932, The Synthesis of Hippuric Acid. A New Test of Liver Function, *Am. J. M. Sc.* **185** 630 (May) 1933

number of cases, comprising a sufficient variety of pathologic changes in the liver to enable one to make a more accurate evaluation of its clinical usefulness

#### PROCEDURE

One hour after a light breakfast of coffee and toast the patient is given 6 Gm of sodium benzoate dissolved in 30 cc of water, preferably flavored with oil of peppermint. This is followed by one-half glass of water. Immediately after taking the drug the patient voids, and he then collects complete specimens of urine hourly for four hours. Should the analysis be delayed more than ten hours, the samples are preserved with toluene. The specimen for each hour is measured and transferred to a beaker. If the volume of any specimen exceeds 100 cc, it is acidified with a few drops of acetic acid and concentrated in a water bath to about 50 cc. Each of the four specimens is acidified with 1 cc of concentrated hydrochloric acid and then tested with congo red paper. If the paper does not turn blue more acid must be added. Each specimen is vigorously stirred until the precipitation of hippuric acid is complete and then is allowed to stand for one hour at room temperature. The crystalline hippuric acid is filtered off on a small filter plate or Buchner funnel, washed with a small quantity of cold water and allowed to dry in the air. The dry samples of hippuric acid are weighed (to the second decimal place is sufficiently accurate). If a balance is not available, the precipitate may be dissolved in hot water and titrated with two-tenths normal sodium hydroxide, phenolphthalein being used as an indicator ( $1 \text{ cc} = 0.0358 \text{ Gm}$  of hippuric acid). To the amount of hippuric acid determined by weight or titration one adds the amount remaining dissolved in the urine. This can readily be calculated, since 100 cc of urine at room temperature will dissolve 0.33 Gm of hippuric acid. Thus, for example, if the hourly specimen amounts to 70 cc and the amount of hippuric acid obtained by weight is 1.1 Gm, the total will be 1.1 plus  $(0.33 \text{ Gm} \times \frac{70}{100})$  or 1.33 Gm of hippuric acid. To express this result in terms of benzoic acid, one multiplies by the factor 0.68. Therefore,  $1.33 \text{ Gm} \times 0.68$  equals 0.91 Gm of benzoic acid.

The normal adult will excrete about 3 Gm of benzoic acid in the form of hippuric acid in four hours. Therefore, 3 Gm has been taken as the normal value for calculating the efficiency of the liver. On this basis the normal range is from 85 to 110 per cent. This provides for the variation due to the size of the individual patient.

#### OBSERVATIONS ON PATIENTS WITH VARIOUS CONDITIONS

*Catarrhal Jaundice*—This common but ill defined clinical condition invariably causes a marked impairment of liver function, as shown in table 1. The observations are in accord with the modern view that the condition is a type of intrahepatic jaundice in which the primary dysfunction is in the parenchymal cell. The results of the test for hippuric acid run roughly parallel with the clinical course. Without special treatment, recovery occurs in from four to six weeks, and at this time the synthesis of hippuric acid is normal. The patient in case 6, who was intensively treated according to the routine, which will be discussed later, recovered promptly, and the reaction became normal in less than two weeks after the onset of the jaundice.

*Toxic Hepatitis of Known Origin*—With the advent of synthetic coal tar compounds as therapeutic agents, the incidence of hepatitis has greatly increased. Clinically I have found it convenient to divide the acute hepatitis into three types, or, perhaps more correctly, stages. The first is enlargement of the liver, sometimes attended by tenderness but without evidence of jaundice. One can look on it as edema of the liver, probably related to angioneurotic edema. Function may not be appreciably disturbed. In fact, a patient from my previous series who had mild hepatitis without jaundice following treatment with arsphenamine had an increased output of hippuric acid, which suggested abnormal stimulation rather than a depression of function. The second type, which is the most common, shows jaundice and usually enlargement of the liver. Hepatic function is definitely diminished, as illustrated by

TABLE 1—*Observations on Patients with Catarrhal Jaundice*

Case	Sex and Age, Years	Enlarge-ment of Liver	Jaundice*	Excretion of Hippuric Acid in Terms of Benzoic Acid, Gm					Percent age of Normal	Comment
				1 Hr	2 Hr	3 Hr	4 Hr	Total		
1	F 21	+	83	0.24	0.38	0.37	0.86	1.85	62	2 months later 1 month later
				0.43	0.41	0.87	0.71	2.42	81	
				0.90	0.91	1.00	0.34	3.15	105	
2	F 60	+	70	0.10	0.17	0.41	0.57	1.25	42	History of an induced abortion 2 months previously 1 month later
3	F 21	+	85	0.15	0.21	0.23	0.28	0.87	29	
				0.55	0.77	0.63	0.60	2.55	85	
4	F 34	+	75	0.17	0.32	0.44	0.68	1.61	54	2 weeks later
5	M 29	0	++	0.37	0.59	0.63	0.60	2.19	73	
6	M 60	0	48	0.14	0.46	0.64	0.56	1.80	60	
				0.60	0.78	1.02	0.83	3.23	107	
7	M 21	0	88	0.21	0.63	0.61	0.43	1.88	63	

\* In this and the following tables the figures indicate the icteric index

the cases in table 2, and in the severe type the function may become very low. The third class is frank yellow atrophy or, perhaps more correctly, massive necrosis of the liver. The condition in case 11 can be considered as bordering on the third stage. Severe hepatitis developed from a single 2 cc dose of carbon tetrachloride given as an anthelmintic. The patient had disregarded her physician's instructions not to eat after taking the drug, and she had neglected to take a saline cathartic. She was extremely toxic and remained delirious for four days, and deep jaundice developed. The clinical indications of severe hepatitis were corroborated by the exceedingly low output of hippuric acid, which was only 17 per cent of normal. The great reparative power of the liver in youth was well illustrated by the rapid clinical recovery and the relatively speedy return to normal of the function of the liver. The patient was, however, treated intensively. Hepatitis with jaundice developed in case 9 following the administration of eight

TABLE 2—*Observations on Patients with Hepatitis of Known Origin*

Case	Sex and Age, Years	Enlarge ment of Liver	Jaun dice	Excretion of Hippuric Acid in Terms of Benzoic Acid, Gm					Percent age of Nor mal	Comment
				1 Hr	2 Hr	3 Hr	4 Hr	Total		
8	F 60	++	0	0 12	0 34	0 52	0 39	1 37	46	Neocinchophen, compli cated by cardiac condition
				0 35	0 46	0 63	0 67	2 11	70	1 month later, after treatment
				0 24	0 47	0 53	0 48	1 72	57	6 months later
9	F 35	++	+	0 31	0 54	0 43	0 44	1 72	57	After 8 doses of neoarsphenamine
10	F 52	0	0	0 52	0 72	0 65	0 75	2 64	88	6 months after recov ery from cinchophen hepatitis
11	F 21	+	++	0 07	0 14	0 21	0 10	0 52	17	After 2 cc of carbon tetrachloride
				0 33	0 49	0 90	0 89	2 61	87	7 weeks later, clinically well
12	M 41	+	70*	0 30	0 58	0 61	0 71	2 20	78	After neoarsphenamine
13	M 26	+	++	0 50	0 86	1 35	0 35	3 06	102	Jaundice persisting 2 months after 2 injec tions of arsphenamine

TABLE 3—*Observations on Patients with a Malignant Process with Metastasis to the Liver*

Case	Sex and Age, Years	Enlarge ment of Liver	Jaun dice	Excretion of Hippuric Acid in Terms of Benzoic Acid, Gm					Percent age of Nor mal	Comment*
				1 Hr	2 Hr	3 Hr	4 Hr	Total		
14	F 53	+	0	0 17	0 50	0 61	0 62	1 90	63	Empyema of gallblad der with beginning ma lignant process (S)
15	F 65	++	10	0 24	0 45	0 50	0 47	1 66	55	Malignant process with metastases to liver (C)
16	M 70	++	0	0 26	0 57	0 71	0 74	2 28	76	Carcinoma of gallblad der and liver (S)
				0 15	0 25	0 41	0 29	1 10	37	1 month later
17	F 67	++	0	0 26	0 46	0 57	0 61	1 90	63	Adenocarcinoma of ovary with metastasis to liver (S)
18	M 62	++	15	0 22	0 66	0 65	0 77	2 30	77	Carcinoma of pan creas with metastasis to liver (S)
19	M 53	++	++	0 19	0 42	0 55	0 58	1 74	58	Carcinoma of stomach with metastasis to liver (A)
20	M 59	++	120	0 16	0 30	0 39	0 39	1 24	41	Carcinoma of the head of pancreas (S)
21	M 59	++	75	0 11	0 13	0 27	0 12	0 63	21	Generalized carcinoma tosis involving liver (A)
22	F 50	+	0	0 14	0 34	0 61	0 45	1 54	51	Abdominal neoplasm with metastasis to liver (C)
23	F 49	0	0	0 51	0 58	0 48	0 54	2 11	70	Carcinoma of ascend ing colon with adhe sion to liver (S)
24	M 48	++	0		1 02	1 63	0 65	3 30	110	Carcinoma of trans verse colon with me tastasis to liver (S)
25	F 65	++	0	0 24	0 62	0 30	0 40	1 56	52	Carcinoma of colon with metastasis to liver (S)
26	M 61	++	60	0 15	0 46	0 57	0 46	1 64	55	Carcinoma of stomach with metastasis to liver (S)

\* In this and the following table the letters in parentheses indicate the method of making the diagnosis clinically (C), surgically (S) or at autopsy (A)



0.3 Gm doses of neoarsphenamine. On investigation of the patient's previous record, it was found that a Wassermann reaction which was anticomplementary had been erroneously interpreted as positive. There was no evidence either clinically or serologically that the patient ever had syphilis. One can therefore look on this case as further evidence for the view that the arsphenamine group of compounds can cause damage to the liver in the absence of the predisposing influence of syphilis.

*Malignant Processes, Metastasis to the Liver*—In all but one of the twelve cases of a malignant process, given in table 3, there was a definite diminution of function according to the test for hippuric acid. The one exception is hard to explain. It seems probable that the disturbance of function is due primarily not to a destruction of parenchymal tissue but rather to the toxins arising from the malignant process. The results of the test appear to run fairly parallel with the clinical condition of the patient. This was illustrated by the patient in case 16, who at the time of his admission to the hospital showed few signs of cachexia and a function 76 per cent of normal. In the course of one month his condition declined rapidly from a clinical point of view, and the hepatic function dropped to 36 per cent.

*Cholecystitis and Cholelithiasis*—Since cholecystitis is essentially an extrahepatic condition, it is to be expected that liver function will not be greatly disturbed. Both in the present series (table 4) and in an earlier group it was noted that the production of hippuric acid was not impaired in cases of cholecystitis, in fact, a number of patients actually showed an abnormally large output. Likewise, obstruction of the common duct by stones, even with a long history of intermittent jaundice, caused no definite impairment of liver function. Vaccaro<sup>2</sup> recently made an interesting study of cholecystitis, correlating the output of hippuric acid with the gross appearance of the liver noted at operation. He observed a fairly close relationship between the results of the test for function and the degree of cirrhosis grossly discernible. From the results obtained by the test for hippuric acid, one can conclude that cholecystitis usually causes little or no diminution of hepatic efficiency and that even obstruction due to a stone in the common duct will have little effect on the liver unless the blockage is complete and unduly prolonged.

*Miscellaneous Hepatic Diseases*—Three patients with atrophic cirrhosis had a marked diminution of function as measured by the synthesis of hippuric acid. The patient in case 47 had also thrombocytopenic

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2 Vaccaro, P. The Synthesis of Hippuric Acid. Its Value in Detecting Hepatic Damage Secondary to Diseases of the Extrahepatic Biliary System, Surg, Gynec & Obst **61** 36 (July) 1935

purpura, which responded to splenectomy, but the patients in cases 48 and 49 had typical advanced Laennec cirrhosis with ascites. Cases 50, 51 and 52 were classified as hypertrophic cirrhosis of unknown origin. The difficulty of arriving at a satisfactory diagnosis is illustrated by the remaining cases in table 5. In case 53 there was a history of recurring attacks of jaundice, with nausea and vomiting, and a marked loss of weight. The patient presented the picture of a toxic rather than an obstructive type of jaundice. It is difficult to decide whether case 54 represents syphilitic cirrhosis or arsphenamine hepatitis. The patient

TABLE 4—*Observations on Patients with Cholecystitis and Cholelithiasis*

Case	Sex and Age, Years	Enlarge-ment of Liver	Jaundice	Excretion of Hippuric Acid in Terms of Benzoic Acid, Gm					Percent age of Normal	Comment
				1 Hr	2 Hr	3 Hr	4 Hr	Total		
27	F 39	0	0	0.73	0.99	1.12	0.75	3.59	120	Cholecystitis (S)
28	F 41	0	0	0.31	0.81	0.99	0.69	2.80	93	Cholecystitis (S)
29	F 65	0	0	0.52	1.14	1.38	0.37	3.41	114	Cholecystitis (S)
30	F 50	0	0	0.46	0.71	0.67	0.82	2.66	89	Cholelithiasis (\ ray) nephrectomy 14 years previously
31	M 56	0	0	0.22	0.40	0.90	0.83	2.35	78	Cholelithiasis (\ ray)
32	M 65	0	0	0.60	0.88	0.99	0.91	3.38	113	Cholecystitis (C)
33	M 34	+	0	0.43	0.75	0.90	0.66	2.74	91	Cholelithiasis and abscess of liver (S)
34	M 31	0	0	0.53	0.64	0.94	0.78	2.89	96	Cholecystitis (S)
35	F 52	0	0	0.34	0.60	0.78	0.73	2.45	82	Pain in upper quadrant on right, cholecystectomy 5 years before
36	M 36	0	0	0.69	0.77	0.53	0.71	2.70	90	Cholecystitis (C)
37	F 53	0	0	0.23	1.17	1.38	0.17	2.95	98	Cholecystitis (C) and asthma
38	F 54	0	30	0.33	0.76	1.15	0.92	3.16	105	Large stone of common duct, liver appeared normal (S)
39	M 49	0	19	0.59	0.75	0.88	0.91	3.13	104	Stone of common duct (S)
40	F 50	0	9	0.28	1.08	0.67	0.63	2.66	89	Cholecystitis (C)
41	M 53	0	0	0.90	0.93	0.86	1.07	3.76	125	Cholecystitis (C)
42	F 37	0	0	0.24	0.84	0.83	0.79	2.70	90	Cholecystitis (C)
43	F 26	+	0	0.73	0.74	0.71	0.92	3.10	103	Cholecystitis (C)
44	F 37	+	15	0.10	1.03	1.23	1.04	3.40	113	Cholecystitis (C) and cholelithiasis, slight obstruction of common duct (S)
45	M 57	0	0	0.27	0.65	0.93	0.93	2.78	93	Cholecystitis (S)
46	F 25	0	0	0.55	0.81	0.80	0.41	2.57	86	Cholecystitis and cholelithiasis, liver appeared normal (S)

in case 55 had toxemia of pregnancy and showed a moderate impairment of liver function. The patient in case 56 had primarily a cardiac disturbance, but it is probable that she had a septic process, as indicated by the chart for the temperature, and that sepsis was responsible for the mild jaundice and the decrease in liver function. Transient jaundice, such as was observed in case 57 following an appendectomy, was not accompanied by demonstrable impairment of liver function. The patient in case 58 presented a very puzzling condition. She had severe diarrhea, a slightly enlarged liver, brown pigmentation, especially on her legs, an icteric index of 60 and no free hydrochloric acid in her stomach. Inter-

estingly, the plasma was markedly anticomplementary.<sup>3</sup> This observation, together with the jaundice pigmentation and enlargement of the liver indicated a hepatic pathologic process but a definite diagnosis could not be made. The output of hippuric acid was very low.

The cases listed in table 5 illustrate that hepatic insufficiency, as measured by the test for hippuric acid, is present in a variety of diseases of the liver. Unfortunately the number of cases of cirrhosis is too small to permit one to arrive at a definite conclusion as to whether diminished function is a concomitant or an essential part of the disease.

TABLE 5—Observations on Patients with Miscellaneous Types of Hepatic Diseases

Case	Sex and Age, Years	Enlargement of Liver	Jaundice	Excretion of Hippuric Acid in Terms of Benzoic Acid, Gm					Percentage of Normal	Comment
				1 Hr	2 Hr	3 Hr	4 Hr	Total		
47	F 38	0	S	0.15	0.20	0.43	0.63	1.41	47	Thrombocytopenic purpura, splenectomy, liver small and nodular
48	F 59	0	0	0.10	0.25	0.33	0.42	1.10	57	Atrophic cirrhosis with ascites
				0.13	0.27	0.29	0.33	1.05	55	1 month later
49	M 51	0	0	0.25	0.60	0.65	0.70	2.20	73	Atrophic cirrhosis with ascites
50	F 51	---	0	0.35	0.47	0.52	0.55	1.92	64	Hypertrophic cirrhosis, tumor of pericardium, diarrhea
51	M 68	---	0	0.23	0.66	0.76	0.71	2.36	79	Hypertrophic cirrhosis, diabetes, alcoholism
52	F 49	---	0	0.33	0.67	0.79	0.65	2.44	81	Hypertrophic cirrhosis
53	F 65	---	15	0.10	0.47	0.57	0.38	2.12	71	Recurrent jaundice, loss of weight, epigastric pain
54	M 53	---	18	0.15	0.24	0.64	0.43	1.46	49	Syphilis treated with bismuth and arsenphenamine
55	F 35	0	0	0.35	0.51	0.58	0.68	2.12	71	Toxemia of pregnancy
56	F 45	---	20	0.13	0.70	0.60	0.72	2.15	72	Enlarged heart, septic temperature
57	M 63	0	12	0.22	0.63	1.02	0.71	2.68	89	Transient jaundice postoperative
58	F 54	—	60	0.12	0.36	0.52	0.58	1.58	53	Diarrhea, brown pigmentation of skin, achlorhydria
				0.17	0.50	0.27	0.23	0.97	32	1 month later

*Nonhepatic Conditions*—In order to establish that the diminished production of hippuric acid is due only to damage to the liver, the test was carried out on a number of patients who had no clinical evidence of hepatic damage (table 6). It can readily be seen that in none of the patients was there a marked lowering of the production of hippuric acid. Two patients who had undergone nephrectomy (cases 30 and 74) showed a normal output. This indicates that one normal kidney can readily excrete hippuric acid as fast as it is produced. It should be mentioned that the kidneys' capacity to excrete hippuric acid is approxi-

3 Quick, A. J. The Relationship Between Complement and Prothrombin. *J. Immunol.* 29:87 (Aug.) 1935.

mately 50 per cent greater than the liver's ability to synthesize the compound. As a consequence, only in cases of severe damage to the kidneys does the test fail as a test of liver function because of renal retention of hippuric acid. Since no allowance was made for this margin

TABLE 6—*Observations on Patients with Diseases Not Involving the Liver*

Case	Sex and Age, Years	Enlarge-ment of Liver	Jaundice	Excretion of Hippuric Acid in Terms of Benzoic Acid, Gm					Percent age of Normal	Comment
				1 Hr	2 Hr	3 Hr	4 Hr	Total		
59	M 47	0	0	0.85	0.95	1.14	0.57	3.51	117	Chronic arthritis
60	F 57	0	0	1.01	1.21	0.98	0.47	3.67	122	Chronic arthritis
61	F 49	0	0	0.45	1.29	1.03	0.69	3.46	115	Chronic arthritis
62	M 39	0	0	0.51	0.46	1.36	0.69	3.02	101	Chronic arthritis
63	F 50	0	0	0.51	0.67	0.77	0.83	2.78	93	Chronic arthritis
64	M 58	0	0	0.61	0.85	0.95	0.84	3.25	108	Chronic arthritis
65	M 37	0	0	0.67	0.89	0.93	0.31	2.80	93	Diarrhea, possible infection with tropical disease, alcoholism
66	M 41	0	0	0.94	1.22	0.93	0.27	3.36	112	Diarrhea, previous history of amebic dysentery
67	M 62	0	0	0.33	0.78	0.93	0.80	2.84	95	Gastro enteritis
68	M 27	0	0	0.52	1.05	0.84	0.45	2.86	95	Gastric ulcer
69	M 41	0	0	0.42	0.95	0.90	0.48	2.75	92	Gastric ulcer
70	M 34	0	0	0.61	1.05	0.92	0.50	3.08	103	Gastric ulcer healed
71	F 40	0	0	0.32	0.68	1.11	1.06	3.17	106	Pernicious anemia
72	F 25	0	0	0.68	0.74	0.80	0.73	2.95	98	Secondary anemia of unknown cause
73	M 33	+	0	0.50	1.04	0.88	0.55	2.97	98	Malaria
74	M 35	0	0	0.48	0.80	0.92	0.96	3.16	105	Nephrectomy 2 weeks before
75	M 32	0	0		0.93	1.04	1.09	3.06	102	Polycythemia
76	M 49	+	0	0.25	1.07	1.10	0.98	3.40	113	Hodgkin's disease
77	F 53	0	0	0.99	1.00	1.02	0.26	3.27	109	Multiple sclerosis
78	M 24	0	0	0.72	0.85	0.91	0.62	3.10	103	Trichiniasis
79	F 27	0	0	0.40	0.86	1.02	0.99	3.27	109	Post partum
80	M 24	0	0	0.86	0.77	0.73	0.35	2.71	90	Neurosyphilis
81	M 25	0	0	0.92	0.93	1.00	0.56	3.41	114	Alcoholism
82	M 54	0	0	0.75	1.20	1.28	0.21	3.44	115	Diabetes, coronary disease
83	F 83	0	0	0.27	0.63	0.85	0.67	2.41	81	Hypertensive heart disease
84	F 67	0	0	0.62	0.82	0.88	0.63	2.95	98	Recurrent attacks of dyspnea, cyanosis
85	F 70	+	0	0.19	1.06	0.80	0.88	2.93	98	Acute cardiac failure
86	F 17	++	0	0.26	0.60	0.74	0.80	2.40	80	Rheumatic heart disease
87	M 59	0	0	0.37	0.90	1.05	0.75	3.07	102	Essential hypertension
88	F 52	0	0	0.78	0.75	1.10	1.27	3.90	130	Needle embedded in liver
89	M 45	0	0	0.37	1.05	1.00	0.58	3.00	100	Excessive use of aminopyrine, acetophenetidin and other drugs
90	F 47	0	0	0.30	0.54	0.90	0.74	2.48	83	Clinical picture suggested gout
91	M 70	0	0	0.86	0.93	0.92	0.33	3.04	101	Moderate arteriosclerosis
92	M 29	0	0	0.44	0.93	1.31	0.42	3.10	103	Deficiency disease
93	F 54	0	0	0.35	0.64	0.85	1.04	2.88	96	Hypertension, dislocated shoulder
94	M 47	0	0	0.26	0.80	0.92	0.74	2.72	91	Diabetes, alcoholism
95	M 48	0	0	0.71	0.94	1.29	0.65	3.59	120	Neurasthenia
96	M 42	0	0	0.72	1.30	0.52	0.44	2.98	99	Prostatic hypertrophy
97	M 51	0	0	0.62	0.96	0.94	0.42	2.94	98	Hypothyroidism
98	M 53	0	0	1.17	0.75	0.82	1.14	3.88	129	Hypothyroidism
99	F 45	++	0	0.52	0.88	0.94	0.39	2.73	91	Cardiac failure, alcoholism
100	F 65	0	0	0.76	1.26	0.68	0.59	3.29	110	Dermatitis (undiagnosed)

of reserve by the various investigators who attempted to utilize the synthesis of hippuric acid as a test of renal function, it is easy to understand why the test failed. Patients with an enlarged liver due to congestive heart failure gave results which were fairly well within normal

limits Unfortunately, the present series contains no cases of hyperthyroidism, but a small number of patients studied by Shorr, Richardson and Wolff <sup>4</sup> gave normal results Hirsheimer <sup>5</sup> has carried out the test on pregnant women and has observed that the production of hippuric acid declines up to the time of labor but immediately returns to normal after delivery The cause of this is not known and requires further study The output of hippuric acid has been normal in cases of myasthenia gravis <sup>6</sup> and of progressive muscular atrophy <sup>7</sup>

#### COMMENT

Hepatic insufficiency can be determined only by a test specifically designed to estimate a physiologic function of the liver The cardinal clinical signs of disease of the liver (change in the size and consistency of the organ and jaundice) are not per se evidence of hepatic insufficiency The liver enlarged because of congestive heart failure may still exhibit normal function, while toxic hepatitis with no demonstrable change in the size of the liver may cause a severe decrease in function Likewise, a patient with intense jaundice due to an obstruction caused by a stone of the common bile duct may have no appreciable disturbance of liver function, whereas another patient with low grade intrahepatic jaundice may show a marked degree of hepatic dysfunction The need of a means for determining hepatic insufficiency is well recognized but does not appear to be met by the tests for liver function now in common use There has been serious doubt whether any empirical test, such as the removal from the blood stream of a dye which is foreign to the body, can adequately serve as a criterion of the liver's efficiency, especially in view of the organ's multiplicity of functions

A test based on the synthesis of hippuric acid should, however, yield a more accurate measure of the liver's ability to do its work In the first place, the test determines an important function, namely, that of detoxication Probably the mechanism that combines benzoic acid with amino-acetic acid is the same as that which unites cholic acid to amino-acetic acid to form glycocholic acid, one of the important acids of bile In the second place, the test depends on the liver's capacity to synthesize

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4 Shorr, E, Richardson, H B, and Wolff, H G Endogenous Glycine Formation in Myopathies and Graves' Disease, *Proc Soc Exper Biol & Med* **31** 207 (Nov) 1933

5 Hirsheimer, A Personal communication to the author

6 Quick <sup>1</sup> Shorr, Richardson and Wolff <sup>4</sup>

7 Freiber, I K, and West, E S Glycine Synthesis in Pseudohypertrophic Dystrophy, *J Biol Chem* **101** 449 (July) 1933 Linneweh, W, and Linneweh, F Zur Frage des Glykokollmangels und der Glykokolltherapie bei progressiver Muskeldystrophie, *Deutsches Arch f klin Med* **176** 526, 1934

amino-acetic acid With the increasing realization of the probable importance of amino-acetic acid in physiology of the muscles and perhaps even in other metabolic processes, any test furnishing information concerning the body's capacity to produce amino-acetic acid should become clinically useful The test for hippuric acid depending thus on two important functions of the liver should give a truer evaluation of hepatic insufficiency than an empirical test The high incidence of diminished production of hippuric acid, especially in cases of chronic hepatic diseases, can be considered as confirmatory evidence The test for hippuric acid offers the distinct advantage that it gives results which seem to correspond fairly closely to the clinical picture and, according to Vaccaro, to the gross pathologic process

Much of the clinical research on function of the liver has had for its object finding a test which would aid in differential diagnosis There is a distinct need for distinguishing between an obstructive type of jaundice, which often requires surgical intervention, and intrahepatic jaundice, which must be treated medically Not infrequently to make an accurate diagnosis is exceedingly difficult, and although laboratory tests are not infallible, they are often helpful From the series of cases presented in this paper it can be seen that the test for hippuric acid gives low results in cases of catarrhal jaundice, acute and chronic hepatitis, usually in cases of a malignant process with metastasis to the liver and in cases of hypertrophic and atrophic cirrhosis and, from earlier studies, syphilitic cirrhosis Normal results are obtained in cases of uncomplicated cholecystitis and cholelithiasis, including obstruction due to stones in the common duct The test therefore is valuable in differentiating between toxic or intrahepatic jaundice and jaundice arising from an obstruction due to a stone in the common duct Certain difficulties, however, cannot be ignored An obstruction of the common duct of long duration may ultimately bring about damage to the liver demonstrable both histologically and functionally Significantly, obstruction due to a malignant process, especially one of the head of the pancreas, will cause a definite diminution of the output of hippuric acid and often also a positive reaction to the test for galactose, as Banks, Sprague, and Snell<sup>8</sup> have observed No differentiation between toxic jaundice and one produced by an obstruction from a malignant growth can be made with certainty on tests of function alone Neither the test for hippuric acid nor any other test can or should be made the sole basis for making a diagnosis The proper correlation of the clinical history with the physical findings and the results of a test for function such as one for the synthesis of hippuric acid, are necessary for arriv-

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<sup>8</sup> Banks, B M, Sprague, P H, and Snell, A M Clinical Evaluation of the Galactose Tolerance Test, *J A M A* **100** 1987 (June 24) 1933

ing at a reasonably correct diagnosis. Every case of jaundice can be profitably studied by the test for hippuric acid, especially if surgical treatment is considered. If the test shows an output below 65 per cent of normal, the possibility of toxic jaundice should be carefully considered.

Usually little difficulty is encountered in differentiating between enlargement of the liver due to congestive heart failure and that due to chronic hepatitis. Nevertheless, there is always the danger of overlooking or mistaking chronic hepatitis for congestion of the liver when signs of cardiac involvement are present. Since the test for hippuric acid gives low results in cases of hepatitis and yields normal figures in cases of uncomplicated cardiac congestion, the test often proves useful.

The test for hippuric acid has definite prognostic value. While it presumably measures hepatic impairment, a low result does not necessarily mean a fatal outcome. The patient in whom severe hepatitis developed from carbon tetra-chloride (case 11) had an output of only 17 per cent, but with prompt treatment the output was restored to nearly normal in six weeks. The test is most useful when repeated to follow the course of the disease. In cases of catarrhal jaundice and acute hepatitis the production of hippuric acid returns to normal as the clinical condition improves. The test is useful in evaluating therapy, and evidence indicates that patients with catarrhal jaundice and various forms of hepatitis can be benefited by a routine treatment which will be discussed later. Certain patients with damage to the liver, however, seem highly refractive to treatment. Thus, the patient in case 48, who had atrophic cirrhosis with ascites, showed no improvement either clinically or according to the test for hippuric acid after intensive treatment for one month.

It is desirable that a test for function contribute toward a broader understanding of the physiology of the organ the efficiency of which it is intended to measure. One of the important functions attributed to the liver is that of detoxication, yet the present knowledge concerning this subject is meager and unsatisfactory. The synthesis of hippuric acid offers one of the easiest and most available means for studying the mechanism of detoxication. Of particular interest is the observation that sodium benzoate consistently depresses the excretion of uric acid. In various types of hepatic injury the retention of uric acid due to sodium benzoate may become very pronounced, as I have recently reported.<sup>9</sup> Such observations clearly indicate that the retention of uric

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9 Quick, A. J. A New Concept of the Significance of Uric Acid in Clinical Medicine, *M. Clin. North America* **17** 1325 (March) 1934, The Effect of Exercise on the Excretion of Uric Acid with a Note on the Influence of Benzoic Acid on Uric Elimination in Liver Diseases, *J. Biol. Chem.* **110** 107 (June) 1935.

acid may occur in the absence of renal disease and furthermore that the liver undoubtedly plays an important rôle in uric acid metabolism. Further investigation concerning the relationship between dysfunction of the liver and retention of uric acid should yield valuable results.

It is not my purpose in this paper to compare the test for hippuric acid with other methods. Nevertheless, some of its advantages should be pointed out. The test does not require intravenous injection, its simplicity makes it available to those who possess only meager laboratory equipment, and it subjects the patient to very little inconvenience. Sodium benzoate, moreover, is a relatively harmless drug, which can be given in the presence of severe hepatic damage without danger of causing further injury or producing serious toxic effects. In fact, the therapeutic doses employed by such clinicians as Senator<sup>10</sup> were larger than the dose used in this test. It should be mentioned that the test is very inexpensive, which strongly recommends it as a routine procedure. The high cost of galactose is a serious obstacle to the wide use of Bauer's test.

#### TREATMENT

The patient with hepatic involvement can often be benefited by proper therapeutic measures. Of greatest importance is the diet. A diet high in carbohydrate has long been regarded as beneficial in cases of hepatic damage. Recently Althausen<sup>11</sup> thoroughly discussed the use of dextrose. Intravenous injection of dextrose seems to be indicated only when it is difficult or impossible to give it orally. If the patient has an intolerance for fat, its intake should be restricted. Often, however, in cases of chronic disease the tolerance can be appreciably increased by the administration of bile salts. Proteins should be supplied mainly in the form of milk. Meat, soup, broth and other meat extracts should not be given, since Bollman and Mann<sup>12</sup> have obtained experimental evidence that meat extracts are distinctly deleterious when hepatic damage exists. It is also well known that meat is badly tolerated by dogs with an Eck fistula. A liberal supply of the antineuritic vitamin should be provided. Vitamin D is also important, because of its relation to calcium metabolism, and is best given in the form of viosterol. Calcium often is very effective in the treatment of acute hepatitis and seems beneficial also in cases of the more chronic type. In cases of acute involvement 10 cc of a 10 per cent solution of calcium gluconate should be administered intravenously daily for from three to four days.

10 Senator, H. Ueber die Wirkung der Benzoesäure bei der rheumatischen Polyarthrit, *Ztschr f klin Med* **1** 243, 1879.

11 Althausen, T. L. Dextrose Therapy in Diseases of the Liver, *J A M A* **100** 1163 (April 15) 1933.

12 Bollman, J. L., and Mann, F. C. Experimentally Produced Lesions of the Liver, *Ann Int Med* **5** 699 (Dec) 1931.



and then from 5 to 10 Gm orally. In chronic cases calcium need be given only orally. The patient should be given 5 Gm of gelatin three times a day. It is best to mix the dry granular gelatin with a little fruit juice just before administering it. Gelatin is rich in amino-acetic acid, which is an important amino-acid that presumably is synthesized mainly by the liver. Since other proteins are relatively poor in amino-acetic acid and since the damaged liver may have an impairment of its synthetic power, it seems logical to supply amino-acetic acid, and this is most economically done with gelatin, which contains 25 per cent of the acid. Furthermore, gelatin is free from the aromatic amino-acids which in instances of intestinal putrefaction are converted to toxic amines and phenols. These are particularly dangerous when the detoxifying function of the liver is diminished.

#### SUMMARY

The excretion of hippuric acid after the administration of sodium benzoate was studied in a series of one hundred cases, in fifty-eight of which hepatic or biliary disease was present. A patient with a normally functioning liver excretes approximately 3 Gm of benzoic acid in the form of hippuric acid in four hours after taking 6 Gm of sodium benzoate. A low output of hippuric acid occurs in cases of catarrhal jaundice and various forms of hepatitis and usually in cases of a malignant process with metastasis to the liver, syphilitic cirrhosis and atrophic and hypertrophic cirrhosis. Reaction to the test is normal in cases of cholecystitis, cholelithiasis and biliary obstruction due to stones in the common duct if the condition is of short duration. The test appears as a promising means for estimating hepatic insufficiency and as an aid in the differential diagnosis, especially in distinguishing between the jaundice of hepatitis and the jaundice arising from obstruction due to a stone in the common duct. The test is useful in following the course of disease of the liver and in determining the effectiveness of therapy. A routine for the treatment of patients with damage to the liver has been outlined.

# THE HEREDITARY FACTOR IN OBESITY

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Definite progress in the treatment of obesity has been made in recent years. Studies in water balance, a better understanding of the glands of internal secretion and their function, a more intelligent conception of dietary requirements and, finally, the pressure of modern fashion, which sends so many stout women to the physician, have all made important contributions to this progress. Yet, when one attempts to classify many cases of obesity, either on an etiologic or on a clinical basis, confusion and uncertainty remain. As early as 1910 Lyon<sup>1</sup> clearly indicated this difficulty, and Jarlov,<sup>2</sup> in his exhaustive work, well illustrated the disagreement and difficulties in classification, even when the etiology was entirely disregarded. If etiology is considered, there is even more confusion. The arguments for endogenous obesity versus exogenous obesity are familiar.<sup>3</sup> The appetite theory, the relationship of occupation to obesity and the depression of metabolism<sup>4</sup> and the dynamic action of food stuff<sup>5</sup> as causes for stoutness have all been studied thoroughly. No one cause by itself explains obesity. However, in this maze of conflicting conceptions and findings, four facts seem to stand out clearly. 1 Obese persons lose weight on a restricted caloric intake. 2 Obesity occurs in patients with hypopituitarism. 3 Obesity occurs in patients with hypothyroidism. 4 Heredity plays more than a coincidental part. To this last fact this discussion will be confined.

That heredity is an important factor in obesity is recognized by most workers in this field. However, it is questionable whether it has

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1 Lyon, I P. Adiposis and Lipomatosis, *Arch Int Med* **6** 28 (July) 1910.

2 Jarlov, E. The Clinical Types of Abnormal Obesity, *Acta med Scandinav*, supp 42, 1932, p 5.

3 Newburgh, L H, and Johnston, M W. Endogenous Obesity. A Misconception, *Ann Int Med* **3** 815 (Feb) 1930. Eidelsberger, Joseph. Obesity with Special Reference to Endocrinopathic Origin, *Ann Int Med* **3** 604 (Dec) 1929.

4 Silver, S, and Bauer, J. Obesity, Constitutional or Endocrine, *Am J M Sc* **181** 769 (June) 1931.

5 Bowen, B D, Griffith, F R, Jr, and Sly, G E. The Effect of a High Fat Meal on the Respiratory Quotient and Heat Production of Normal and Obese Individuals, *J Nutrition* **8** 432, 1934.

received sufficient emphasis in medical discussions. The findings of Davenport<sup>6</sup> seem definitely to indicate that body build follows the mendelian laws of inheritance. By studying the progeny of parents of similar and dissimilar builds, he concluded that there are three gametic factors, of which one may correspond to dystrophy of the thyroid, and one to dystrophy of the pituitary and the third may be a metabolic factor that affects the actual metabolism of the cells themselves. If this hereditary factor is accepted, the onset of obesity in one person as opposed to that in another who is subject to the same environmental influences and is even receiving the same diet may be more readily understood.

Seventy-five stout women were studied in the outpatient department of the Buffalo General Hospital with three points in mind: (1) the factors associated with the onset of obesity as compared with the same factors occurring in a nonstout control group, (2) the incidence of obesity in the parents of the stout group as opposed to that in the parents of the nonstout control group, (3) the body build of the progeny of different matings with special reference to mendelian inheritance of build.

Who is stout and who is merely heavyset is an important and difficult question. I interviewed each patient individually and chose only those who were unquestionably stout for this study. Davenport's<sup>6</sup> figures for age and height were used as standards, each patient being over 15 pounds (6.8 Kg.) heavier than the average for her particular age and height. Originally, the patients in the stout group were subdivided, according to their weight, into stout and excessively stout groups but as the findings were approximately the same in those two groups, they have been combined as merely the stout group for purposes of simplification. In many cases the statement of the patient had to be taken as to the build of the members of her family, introducing, of course, a definite source of error. However, when there was any reasonable doubt, that history was discarded.

Fifty-five women who were definitely not stout were chosen at random as controls. Patients with any debilitating illness were not included. The control patients came from approximately the same age group and had approximately the same incidence of operations and pregnancies—the two most common factors apparently associated with the onset of obesity (tables 1 and 2).

Eighty-three per cent of the stout group were between 21 and 50 years of age, which includes the period of childbearing and the menopause. Eighty-six per cent of the nonstout group were in this same age period. Sixty-one per cent of the stout group and 50 per cent

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<sup>6</sup> Davenport, C. B. *Body-Build and Its Inheritance*, Washington, D. C., Carnegie Institution of Washington, 1923.

of the control group had had one or more pregnancies. Thirty-six per cent of the stout group and 47 per cent of the nonstout group had had operations. Thus the two groups may be compared, being from approximately the same age period and having had approximately the same number of pregnancies and operations.

Sixty-three women in the stout group gave a reliable history as to the onset of obesity. Of the 41 of these who bore children, or 65 per cent, 29, or 71 per cent, stated a direct association between pregnancy and the onset of obesity. Of the 24 who had major operations, or 38 per cent, 7, or 29 per cent, stated a direct association between the operation and the onset of obesity. Of the remaining 27 patients, 4 associated the onset of obesity with puberty and 2 with the menopause, 8 maintained they were "always stout" and 13 apparently had no determinable factor associated with the onset of obesity. Thus, in

TABLE 1—*Age Distribution of Stout and Control Groups*

	Decade					
	Second	Third	Fourth	Fifth	Sixth	Seventh
Stout	6	15	21	24	4	2
Nonstout	1	19	17	8	5	1

TABLE 2—*Causes of the Onset of Obesity in Women*

Pregnancy	Operation	Puberty	Menopause	"Always Stout"	Miscellaneous Causes
29	7	4	2	8	13

67 per cent of the stout group, the onset of obesity was apparently associated with some physiologic or physical episode. However, in another group of women of approximately the same age period and subject to the same physiologic and physical episodes, obesity did not occur.

When one studies the builds of the parents of the stout and the control group a very definite and real difference in the incidence of obesity is apparent (table 3). Of the 61 stout women whose family history seemed unquestionably reliable, 26, or 43 per cent, had a stout mother, 9, or 15 per cent, had a stout father, and 15, or 25 per cent, had both a stout mother and a stout father, making a total of 50, or 82 per cent, having either one or both parents stout. In contrast to this, of the 47 nonstout patients with an equally reliable family history, 14, or 30 per cent, had a stout mother, 1, or 2 per cent, had a stout father, and 3, or 6 per cent, had both a stout mother and a stout father, making a total of 18, or 38 per cent, with either one or both parents stout, as opposed to 82 per cent in the stout group.

If build is inherited, as it seems to be from these figures, this inheritance must be along mendelian lines, as there is probably no other kind of inheritance.<sup>7</sup> A study of inheritance in human beings is, of course, exceedingly difficult because so few generations are available for observation. However, if segregation, which is the indispensable condition of the mendelian theory, can be shown, it follows inescapably that mendelian inheritance is present. Segregation is the dissociation of two unit characters from each other in the course of the formation of the germ cells. Thus, evidence for segregation in human inheritance is a difference in variability of the progeny of different matings.<sup>6</sup>

A study of the progeny of different matings in this group shows a definite difference in variability (table 4). There were 89 offspring from matings of stout persons, 65, or 73 per cent, of whom were stout,

TABLE 3—*Incidence of Obesity in the Parents of Patients in the Stout and in the Control Group*

Group	Mother Stout	Father Stout	Mother and Father Stout	Mother and Father Nonstout
Stout	26	9	15	11
Nonstout	14	1	3	29

TABLE 4—*Data on the Variability of the Progeny of Different Matings*

Matings	Stout Progeny	Nonstout Progeny
Stout and stout	65	24
Stout and nonstout	70	100
Nonstout and nonstout	16	160

and 24, or 27 per cent, of whom were not stout. Of the 170 offspring of matings of a stout and a nonstout person, 70, or 41 per cent, were stout, and 100, or 59 per cent, were not stout—a marked variability. Of the 176 offspring of matings of nonstout persons, only 16, or 9 per cent, were stout, in contrast to the 160, or 91 per cent, who were not stout. Thus, there is present a marked difference in variability in the progeny of different matings, with the offspring of a stout and a nonstout parent the most variable and the offspring of nonstout parents the least variable. The fact that the offspring of stout parents are more variable than those of nonstout parents suggests, as pointed out by Davenport, that stout persons carry gametes for slenderness whereas nonstout persons rarely carry gametes for stoutness. As a corollary to this, regression to a more normal build as a result of these gametes for

<sup>7</sup> Conklin, E. G. *Heredity and Environment*, ed. 3, Princeton, N. J., Princeton University Press, 1920, p. 107.

slenderness can be seen in the offspring of stout parents to a considerably greater degree than in the offspring of slender parents

There appears to be no definite dominance in the series, which, of course, is not essential in mendelian inheritance

#### CONCLUSIONS

Pregnancy or a major operative procedure appeared to be the most common factor associated with the onset of obesity in a group of 63 stout women

Obesity did not develop in another group of women from approximately the same age group and with approximately the same incidence of pregnancies and operations

The incidence of obesity in the parents of the stout group was markedly greater than in the parents of a group of nonstout women

A study of the progeny of different parents indicates segregation, which is evidence for mendelian inheritance of build

It is suggested that consideration of the hereditary factor in obesity may help to explain the apparent inconsistency of build in persons subject to the same environmental influences

# RECOVERY FROM GENERALIZED AMYLOIDOSIS SECONDARY TO PULMONARY TUBERCULOSIS

## REPORT OF A CASE

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Recovery from amyloidosis in a patient with chronic progressive pulmonary tuberculosis is a clinical curiosity. While it is true that experimentation with animals<sup>1</sup> and clinical observations<sup>2</sup> have repeatedly demonstrated that amyloid tissue can undergo spontaneous absorption if the causative agent is removed, unfortunately the tuberculous patient with amyloidosis rarely recovers from the primary process. The following is a report of a case of clinical cure of generalized amyloidosis secondary to extensive pulmonary tuberculosis and tuberculous pyothorax. The patient has been under my observation for the past four years, during which time the entire cycle of development and regression of the amyloid process has been carefully followed.

## REPORT OF CASE

A K, a 34 year old man, was admitted to the country sanatorium of the Montefiore Hospital in August 1931, with a history of a productive cough and fever of five months' duration. Examination disclosed a fibrocaseous infiltration of the entire right lung, with a large cavity in the hilar region and an exudative infiltration in the midzonal portion of the left lung. The sputum contained tubercle bacilli. The temperature ranged between 100 and 102 F. Pneumothorax was induced on the right side and was continued effectively for two and a half months, at the end of which time an effusion occurred. Examination of the fluid showed it to be purulent, with many tubercle bacilli and gram-positive cocci and bacilli. Pneumothorax was discontinued and was replaced by aspiration of the pus, but the condition was progressive, and in January 1932 an empyema necessitatis perforated through the eighth intercostal space in the midscapular line.

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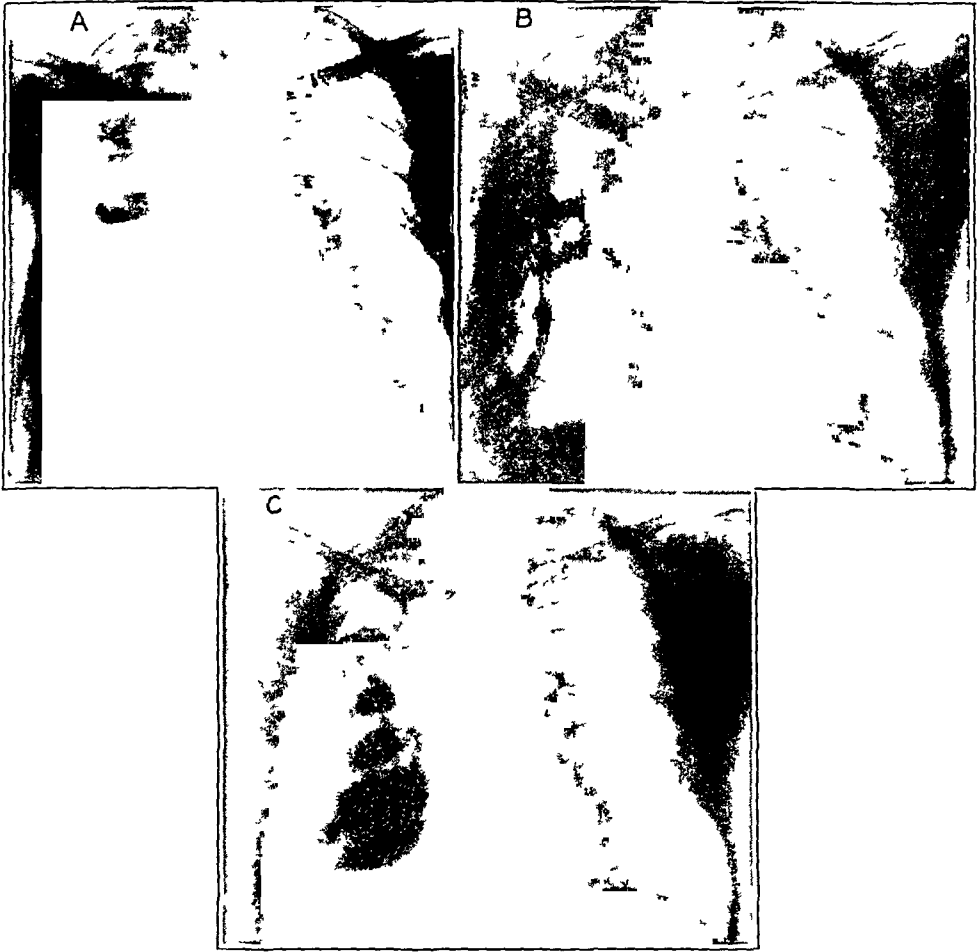
\* Sigmund M. Lehman, Fellow

From the tuberculosis division of the Montefiore Hospital

1 Kuczynski, M. H. *Neue Beitrage zur Lehre vom Amyloid*, Klin Wchnschr **2** 727 (April 16) 1923, *Weitere Beitrage zur Lehre vom Amyloid*, *ibid* **2** 2193 (Nov. 26) 1923.

2 Fagge, C. *The Principles and Practice of Medicine*, Philadelphia, P. Blakiston's Son & Co., 1886, vol. 2, p. 489. Gairdner, W., in discussion on Delafield, F. *Diseases of the Kidneys*, Tr. A. Am. Physicians **6** 149, 1891. Herringham, W. P. *Kidney Diseases*, New York, Oxford University Press, 1912, p. 353. Walker, G. F. *Case of Recovery from Amyloid Disease*, *Lancet* **2** 120 (July 21) 1928.

The patient was transferred to the city institution in March 1932, in a very toxic condition, with the temperature fluctuating between 99 and 104 F. Roentgenograms showed the effusion to be at the level of the seventh rib in the mid-axillary line, with a small area of pneumothorax above the line of the fluid. In the left lung there were visualized many small cavities in the upper lobe and discrete tubercles scattered throughout the lower lobe. Treatment consisted of aspirations of from 400 to 800 cc of pus twice weekly, followed by the instillation of a 10 per cent concentration of a cajaput oil (from *Melaleuca viridiflora*). No improvement was noted with respect to either the local or the constitutional manifestations.



*A* Roentgenogram of the chest showing pyopneumothorax of the right lung and extensive fibrocaseous cavitary involvement of the left lung on May 16, 1932. *B* On Dec 28, 1932, the thoracotomy tube had completely drained the right pleural cavity, the pleura was thickened, and parenchymal lesions were visualized. There was an increase of infiltrations in the lower lobe of the left lung. *C* On Oct 18, 1935, the fluid in the right side of the chest had been drained completely. The roentgenogram shows marked evidence of absorption and fibrosis in the upper lobe of the right lung and considerable clearing in the left lung.

On May 20, 1932, a simple thoracotomy was done with the area under local anesthesia, and a rubber catheter was inserted in the seventh interspace in the posterior axillary line. About a gallon (3.8 liters) of pus was removed at the time of operation, and subsequently there was free drainage through the tube.



The fever persisted for several weeks, but by July a definite improvement was noted, which has continued up to the present time. In January 1933 the patient became afebrile, and since August 1933 the results of examination of the sputum have all been negative. He was discharged from the hospital in August 1934 and has since been followed in the outpatient department. At the time of writing (May 1935) there is drainage of about 0.5 cc of pus daily through the sinus of the thoracotomy wound, the tube having been removed two years before. His general condition is excellent, and since the operation he has gained over 50 pounds (22 Kg) in weight. Serial roentgenograms (illustration) showed complete absorption of the fluid from the right side of the chest and marked improvement of the condition in the left lung.

## COMMENT

The lengthy period of observation of this patient (almost four years) has enabled me to study accurately both the onset and the regression of the amyloid changes. The table depicts the course of the entire amyloid process in terms of retention of congo red, physical signs and findings in the blood and urine.

*Clinical Manifestations of Amyloid Progression and Regression*

Date	Retention of Congo Red, Per centage	Hepato megal	Spleno megal	Edema	Albumin in Urine (Gm Daily)	Serum Proteins (Gm per 100 Cc)		Urea Nitrogen
						Albumin	Globulin	
7/32	54	+	0	0	5	2.96	2.36	11.2
10/32	90	++	+	+	9	1.96	2.36	
2/33	100	+++	++	++	10	1.97	2.17	
8/33	75	+++	++	++	7	2.90	1.76	14.4
7/34	45	+++	+	++	2			
11/34	28	++	+	+	2			
1/35		+	0	+	2	3.22	3.48	15.6
4/35	10	0	0	0	1.75			

Study of the table brings forth many interesting points. First, healing of the tuberculous disease did not immediately initiate regression of the amyloid process. As a matter of fact, progression was most marked during the last six months of 1932, at the time that the pathologic condition of the lungs and the constitutional symptoms were showing marked improvement. The first test with congo red, in July 1932, showed 54 per cent retention in the tissues, just enough to enable a positive diagnosis of amyloidosis to be made, and at that time the only significant clinical finding was albuminuria. Four months later, despite the improvement in the tuberculous condition, there was almost complete retention of the dye (90 per cent), and both the liver and the spleen were palpable. In addition, there were peripheral edema and other associated manifestations of the nephrotic syndrome indicating extensive renal involvement.<sup>3</sup> From August 1933 to the present the retention of congo red diminished steadily until at the last deter-

<sup>3</sup> Rosenblatt, M. B. Clinical Manifestations of Amyloidosis, *Ann Int Med* 8: 678 (Dec.) 1934.

mination, in April 1935, the reading was only 10 per cent. It is to be noted that in November 1934, when the retention was 28 per cent, a figure within the normal range, hepatomegaly, splenomegaly and edema were still observed. At the time of writing the only clinical finding is albuminuria, which is relatively slight. The proteins of the blood serum have been completely restored. Despite the clinical evidence of extensive renal involvement for three years, there has been no impairment of renal function at any time.

During the last year of his hospitalization the patient was given liver therapy, but it is felt that the regression of the amyloidosis could be more properly attributed to the improvement in the tuberculosis than to the effects of the specific treatment.

# FURTHER DATA ON ARTIFICIAL PNEUMOTHORAX IN EXPERIMENTAL LOBAR PNEUMONIA

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AND

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The optimistic reports of numerous foreign clinicians on the use of therapeutic pneumothorax in cases of lobar pneumonia and the encouraging results obtained by us in our first experimental study on dogs<sup>1</sup> have prompted a number of American physicians to resort to artificial pneumothorax in the treatment of lobar pneumonia. The present clinical status of this procedure has recently been presented.<sup>2</sup> No further experimental work on animals has been published, and no studies on patients have been made in an effort to explain the *modus operandi* of this treatment, except those of Blake, Howard and Hull.<sup>3</sup>

These authors studied the agglutinins of the serum of twenty-two patients and found that "agglutinins apparently appear in the blood just about the same as they do in the untreated cases." This is significant, because in some of the cases clinical recovery as judged by the usual criteria occurred as early as six days before there was an appreciable response of the antibodies.

During the past year we have pursued three lines of investigation, hoping by these means to shed light on the reasons for the clinical phenomena frequently observed when artificial pneumothorax is employed in the treatment of lobar pneumonia, both in the experimental animal and in man.

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From the Thoracic Section of the Medical Division, the Hospital of the University of Pennsylvania.

Read before the Section on Practice of Medicine at the Joint Session of the American Medical Association and the Canadian Medical Association, Atlantic City, N J, June 12, 1935.

The experimental work was concluded in the Laboratories of Bacteriology and Surgical Research of the University of Pennsylvania School of Medicine. The study was aided by a grant from the Faculty Research Committee of the University of Pennsylvania.

1 Lieberman, L M, and Leopold, S S. Therapeutic Pneumothorax in Experimental Lobar Pneumonia in Dogs, *Am J M Sc* **187** 315 (March) 1934.

2 Leopold, S S, and Lieberman, L M. The Present Status of Artificial Pneumothorax in the Treatment of Lobar Pneumonia, *Ann Int Med* **9** 19 (July) 1935.

3 Blake, F G, Howard, M E, and Hull, W S. The Treatment of Lobar Pneumonia by Artificial Pneumothorax, *Tr A Am Physicians* **49** 119, 1934.

This presentation is concerned with the following problems (a) the time of appearance of specific antibodies in the blood of dogs in which lobar pneumonia was induced, both those not treated and those treated with artificial pneumothorax, (b) the effect of pneumothorax on lymphatic drainage in the lungs of uninfected rats, and (c) the effect of artificial pneumothorax on experimental bacteremia in dogs induced by the pneumococcus

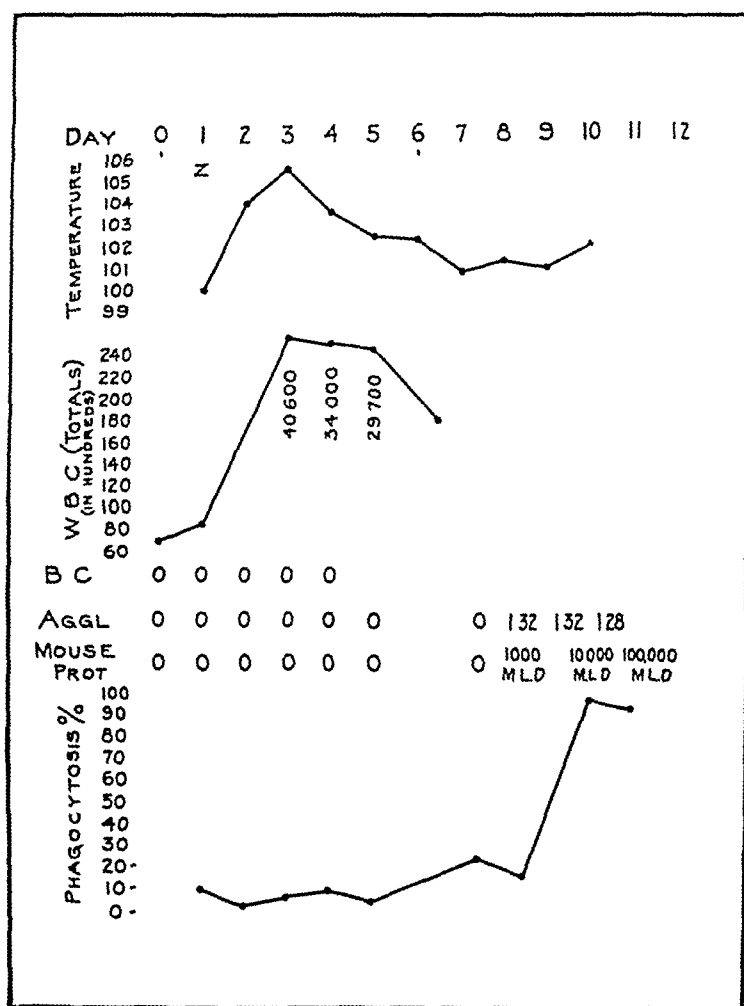


Fig 1 (dog 667B) —Temperatures, leukocyte counts, blood cultures (BC) and results of serum agglutination (AGGL), mouse protection and phagocytosis tests during experimental lobar pneumonia induced in an untreated dog. In this chart  $\alpha$  marks the time of injection.

#### TIME OF APPEARANCE OF SPECIFIC ANTIBODIES IN BLOOD OF DOGS WITH LOBAR PNEUMONIA, BOTH THOSE NOT TREATED AND THOSE TREATED WITH ARTIFICIAL PNEUMOTHORAX

In collaboration with the laboratory of bacteriology, we produced lobar pneumonia in dogs with type I pneumococcus by a modified Robertson technic<sup>1</sup>. In addition to the usual clinical observations, cultures of the blood, determinations of serum agglutination, mouse protection tests and estimations of the phagocytic

power<sup>2</sup> of whole blood were made The last test was carried out by the method recently described by Boerner and Mudd<sup>4</sup> In brief it is performed as follows Venous blood is added to purified heparin and placed in an agitator bath kept at a temperature of between 37 and 38 C To this is added the suspension of bacteria At intervals of three minutes sufficient blood is removed by a capillary pipet, without stopping the agitator, to make the usual blood smears These are fixed and stained by the Giemsa method The results are expressed in terms of the percentages of positive cells, i e, those which show bacteria within the cytoplasm Curves are obtained by plotting the percentage of positive cells against the time intervals Our curves are those obtained after fifteen minutes It was

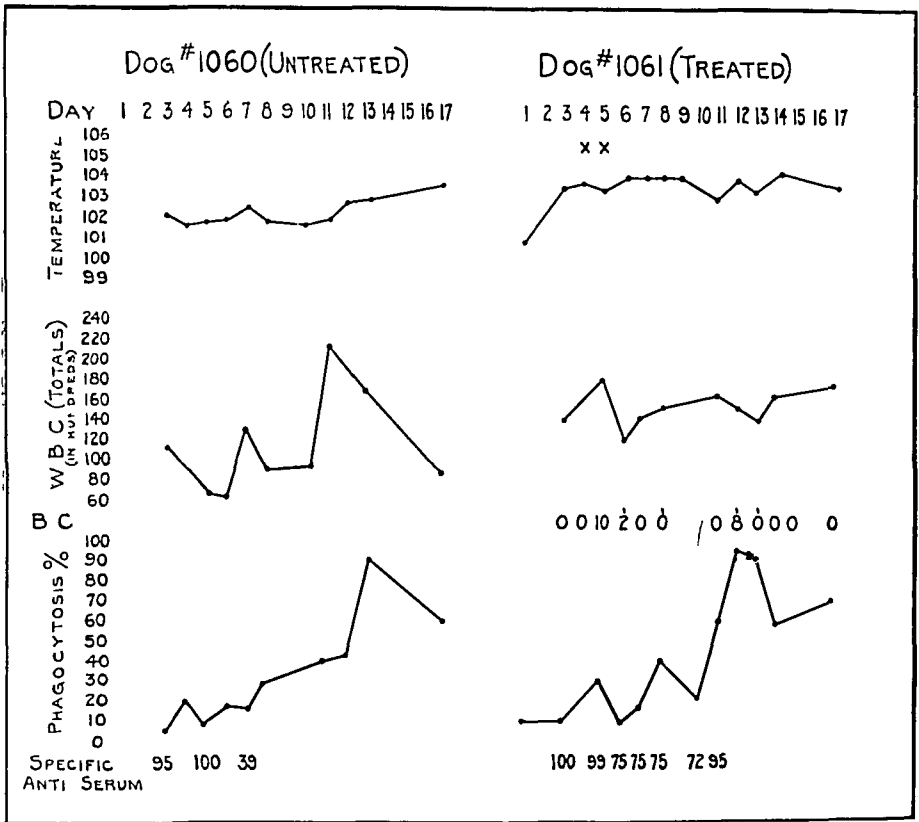


Fig 2—Temperatures, leukocyte counts, blood cultures (BC) and results of the phagocytosis tests during experimental lobar pneumonia induced in an untreated dog and in one treated (dog 1,061) with artificial pneumothorax. In this chart and in the graph shown in figure 3,  $\downarrow$  indicates the time at which pneumothorax was given

soon ascertained that, while the results of the phagocytosis test corresponded with those of the mouse protection test and with those of the determinations of agglutinins, it was more delicate than either. The results of the latter tests were therefore discarded in favor of the estimations of phagocytosis

4 Roerner, F, and Mudd, S. Determination of Phagocytic Power of Whole Blood or Plasma-Leukocyte Mixtures for Clinical or Experimental Purposes, Description of an Improved Method with Representative Findings, *Am J M Sc* 189 22, 1935

Untreated animals were studied first, and it was found that usually before infection and for the first few days thereafter the amount of phagocytosis-promoting antibodies was negligible and that for the next few days it remained well below 50 per cent. Thereafter, the percentage gradually increased, and between the tenth and the fourteenth day it rose abruptly to nearly 100 per cent and remained there. Treatment with artificial pneumothorax did not alter the phagocytic power of the animal's whole blood. In order to check the test for both the untreated and the treated animals, specific type I antipneumococcus serum in a dilution of 1:50 was added to otherwise similarly prepared tubes. With the exception of a single low value these tubes showed marked phagocytosis (from 72 to 100 per cent).

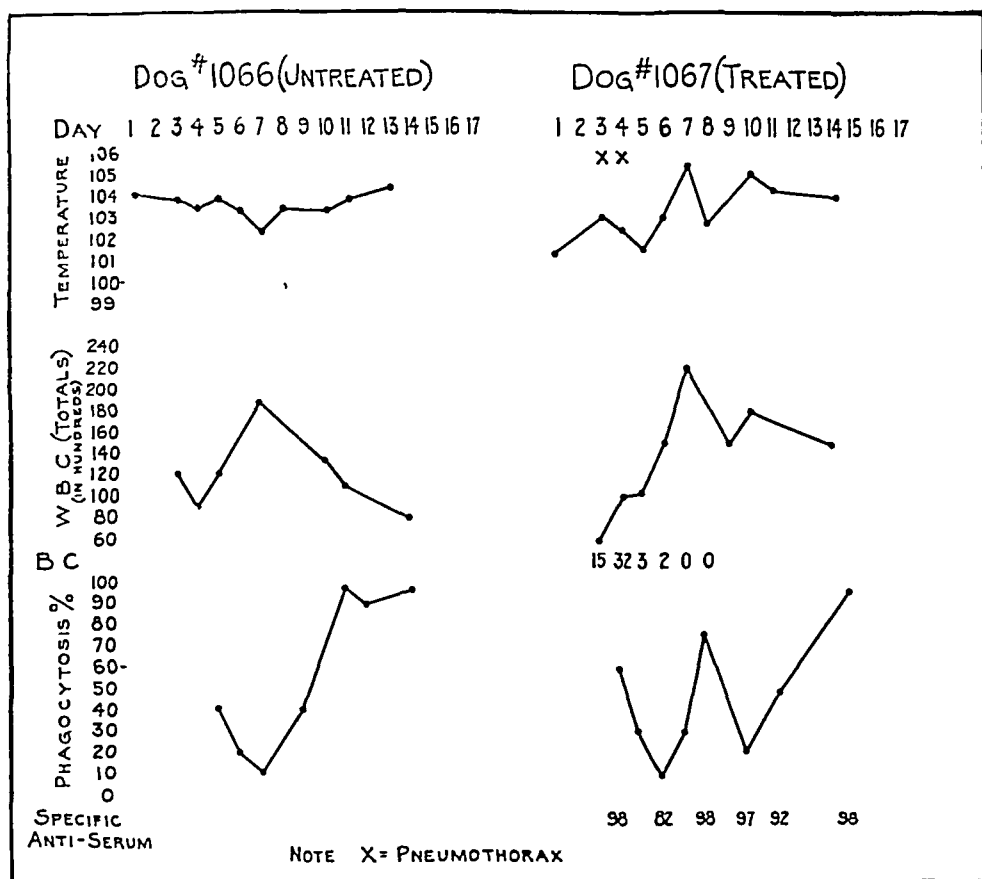


Fig 3—Temperatures, leukocyte counts, blood cultures (BC) and results of the phagocytosis tests during experimental lobar pneumonia in an untreated dog and in one treated with artificial pneumothorax

#### EFFECT OF ARTIFICIAL PNEUMOTHORAX ON LYMPHATIC DRAINAGE IN LUNGS OF UNINFECTED RATS

Dr Henry Hopkins, of the clinic for thoracic diseases, and Dr John Griffith, of the Robinette Foundation of the Hospital of the University of Pennsylvania, have studied the effect of artificial pneumothorax on the lymphatic drainage in the lungs of uninfected rats. Thorium dioxide was injected through the wall of the chest into the parenchyma of each lung near the base, the symmetry of the injections being checked by roentgenograms. One lung was then collapsed. The spread of thorium dioxide was observed by a series of roentgenograms. After

considerable time this substance was rejected because of technical difficulties, and at present other roentgenographically opaque substances are used which appear to have a slower rate of spread. With the use of suspensions of carbon it has been possible to show a decrease in the amount and the extent of the spread, both grossly and microscopically, in the collapsed lung. The regional lymph nodes also showed a distinct difference between the two sides. In the expanded lung the lymphatics of the parietal pleura and the diaphragm showed considerable carbon, whereas there was little on the side of the collapsed lung.

Although the work is still incomplete, there is evidence to show that pneumothorax definitely decreases the amount and the rate of spread of foreign material from the collapsed lung to the adjacent lymphatics. Similar observations have been reported by Shingu,<sup>5</sup> who exposed rabbits to atmospheres of soot before and after producing artificial pneumothorax, and by White and Gammon,<sup>6</sup> who injected oil colored with sudan into the jugular veins of experimental animals and then studied the distribution of pigment in the collapsed and in the fully expanded lungs. There is, therefore, considerable evidence that particulate matter is retained in the compressed lung, its absorption being retarded by obstruction of the lymphatic vessels. Similarly, it is conceivable that the good effects of compression therapy in the early stages of clinical and experimental lobar pneumonia may be due to the retardation of the dissemination of toxic products or bacteria, or both, from the diseased lung to the adjacent lymphatics.

#### EFFECT OF ARTIFICIAL PNEUMOTHORAX ON EXPERIMENTAL BACTEREMIA IN DOGS INDUCED BY PNEUMOCOCCUS

We were encouraged to pursue this study because in our first publication we reported on one animal (dog 1,023) which was treated and recovered, despite an overwhelming invasion of the blood stream. In this connection, it is of interest that Robertson and his associates,<sup>7</sup> who produced experimental lobar pneumonia with *Pneumococcus* in more than one hundred dogs, all untreated, stated that only one dog with a blood culture showing more than 50 colonies per cubic centimeter recovered.

In an effort to determine the proper dosage of pneumococci for inoculation varying amounts of culture were used in order to obtain the greatest number of

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5 Shingu, Susuo. Beitrag zur Physiologie des kunstlichen Pneumothorax und seiner Wirkung auf die Lungentuberkulose, Beitr z Klin d Tuberk **11** 1, 1908.

6 White, W. C., and Gammon, A. M. Some New Features of Interest About the Pulmonary Circulation and the Fate Therein of Intravenously Introduced Fats, Tr Nat A Prev Tuberc **10** 215, 1914.

7 Terrell, E. T., Robertson, O. H., and Coggeshall, L. T. Experimental Pneumococcal Lobar Pneumonia in the Dog. Method of Production and Course of the Disease, J Clin Investigation **12** 393, 1933.

positive blood cultures compatible with the continuation of life for at least forty-eight hours. With injection of 0.1 cc of sedimented pneumococci of type I bacteremia developed in 70 per cent of the dogs, with 0.125 cc the incidence was 75 per cent, with 0.2 cc, 92 per cent, and with 0.25 cc and 0.3 cc, 100 per cent.

In our previous work, with the use of 0.06 cc of sedimented pneumococci of type I or type III, six of eighteen treated dogs had bacteremia. All these animals, including dog 1,023, with a blood culture containing an uncountable number of colonies, recovered. Of the group of eighteen untreated dogs used as controls, eight showed bacteremia during life, and only one recovered. Pneumococci were noted post mortem in the blood of the hearts of two others. The results in the two groups cannot be compared, because six of the nine dogs with bacteremia

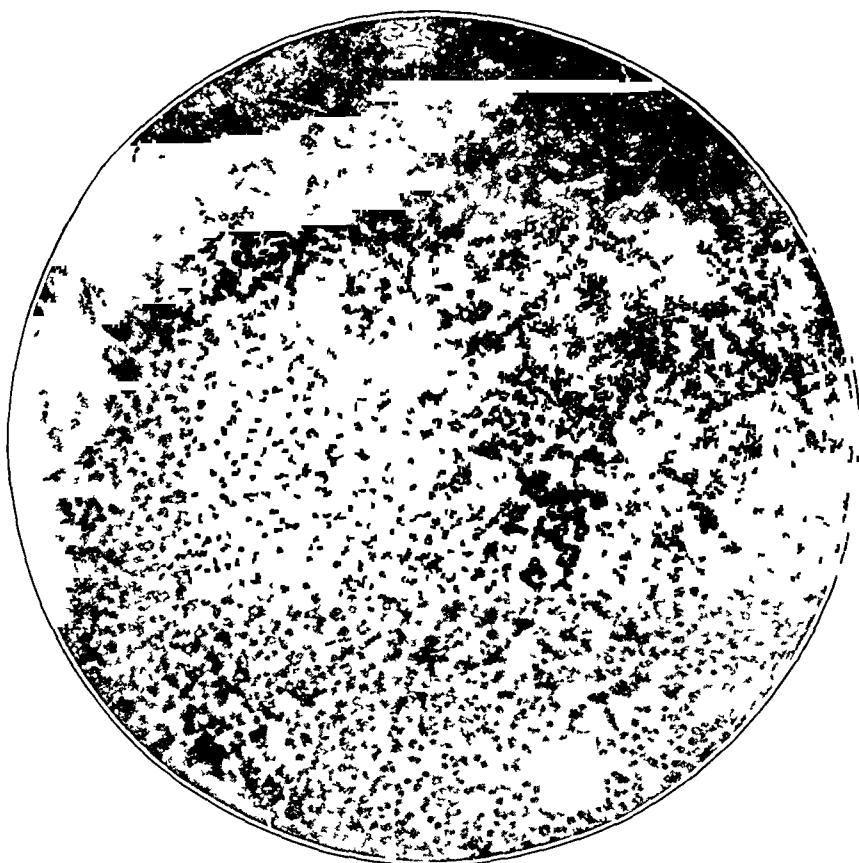


Fig. 4 (dog 523) —Colonies obtained from 1 cc of the blood culture on the second day of the disease before the first treatment. Death occurred on the sixth day.

which died succumbed within forty-eight hours and therefore could not have been given pneumothorax.

In our present group thirteen dogs with bacteremia were treated and of these seven recovered and six died. The culture of the blood of one of the animals which recovered revealed 32 colonies, and that of another, 62 colonies per cubic centimeter. Four of the six dogs which died had an overwhelming invasion of the blood stream and in two of these autopsy revealed involvement of both lungs. Similar postmortem observations were reported by Robertson<sup>7</sup> for a large number of animals which were given an overwhelming infective dose.

The magnitude of the invasion of the blood stream in one of our treated animals which died (dog 523) is shown in figure 4.



The untreated control group consisted of twenty-three dogs with bacteremia, thirteen of which cannot be compared with those of the treated group, because they died within the first forty-eight hours. Of the remaining ten animals, six recovered, and four died. For those which recovered, the maximum number of colonies, respectively, ranged from 2 to 7 per cubic centimeter. No untreated dog with a culture showing more than 7 colonies survived.

TABLE 1—Data on Treated Dogs with Bacteremia

Dog No	Amount of Culture Injected, Cc	Maximum No of Colonies per Cc	Comment
213	0.1	+	Recovered
725	0.1	Uncountable	Died on 4th day, both lungs involved
668	0.125	3	Recovered
671	0.125	8	Recovered
690	0.125	15	Recovered
427	0.2	8	Died on 6th day
456	0.2	Uncountable	Died on 5th day
523	0.2	Uncountable	Died on 6th day, both lungs involved
476	0.25	2	Recovered
436	0.3	Uncountable	Died on 3rd day
319	0.5	62	Recovered
1,061	0.5	10	Died on 19th day, both lungs involved
1,067	0.5	32	Recovered

TABLE 2—Data on Untreated Dogs with Bacteremia

Dog No	Amount of Culture Injected, Cc	Maximum No of Colonies per Cc	Comment
617	0.1	4	Recovered
618	0.1	2	Recovered
709	0.1	9	Died on 2nd day
713	0.1	4	Died on 27th day, both lungs involved
721	0.1	6	Died on 2nd day
669	0.125	4	Recovered
670	0.125	4	Died on 22nd day (no autopsy)
754	0.125	7	Recovered
755	0.125	8	Died on 3rd day
788	0.125	+	Died on 2nd day, both lungs involved
791	0.125	Heavy growth	Died on 2nd day, both lungs involved
460	0.2	4	Died on 2nd day
461	0.2	3 (late in 5th day)	Recovered
521	0.2	20	Died on 2nd day, both lungs involved
522	0.2	7	Died on 2nd day, both lungs involved
543	0.2	6	Recovered
544	0.2	About 300	Died on 3rd day
545	0.2	Heavy growth	Died on 2nd day, both lungs involved
546	0.2	Heavy growth	Died on 2nd day
473	0.25	8	Died on 2nd day
474	0.25	16	Died on 2nd day
475	0.25	9	Died on 2nd day, both lungs involved
437	0.3	4	Died on 2nd day

In our earlier series there was not a single instance of late development of bacteremia in any animal in which treatment was instituted when the blood culture was negative. In the present series, at the time when the production of antibodies was studied a number of dogs without bacteremia were treated. One of these animals (dog 1,061) was given pneumothorax on the second day, at which time the culture of the blood was sterile. Bacteremia appeared on the next day, and then subsided and reappeared on the twelfth day. The dog died on the nineteenth day. Autopsy revealed pneumonia of both lungs. In this instance compression therapy did not prevent bacteremia.

Although in most animals with bacteremia in this series artificial pneumothorax appeared to produce a coincident diminution in the number of colonies, the blood culture for one animal (dog 456) revealed 6 colonies per cubic centimeter on the second day, and, despite treatment, overwhelming invasion of the blood stream occurred on the third day. Death took place on the fifth day. In this case pneumothorax did not control bacteremia.

#### SUMMARY AND CONCLUSIONS

In experimental pneumococcic lobar pneumonia in dogs, the time of appearance of specific antibodies, as determined by mouse protection, agglutination and phagocytosis tests, was uninfluenced by the use of artificial pneumothorax. The results obtained for the treated and for the untreated animals of the control group were practically identical. This corroborates the clinical findings of Blake, Howard and Hull.<sup>3</sup>

Experimental work is still in progress on the effect of artificial pneumothorax on lymphatic drainage in the lungs of uninfected rats. These and similar researches suggest by analogy that when artificial pneumothorax is used in the treatment of lobar pneumonia it may retard the absorption of toxins and organisms by the lymphatics.

No definite statement is permissible at this time in respect to the effect of artificial pneumothorax on pneumococcic bacteremia. With a single exception which occurred in our preceding series, compression therapy was ineffective in the presence of overwhelming invasion of the blood stream. However, it may be significant that no untreated animal recovered in which the blood culture showed more than 7 colonies per cubic centimeter, whereas in the treated group one dog with 32 and one with 62 colonies per cubic centimeter survived.

While this experimental study was in progress the following statement was made in a clinical presentation,<sup>2</sup> and we wish to repeat it: "Much more experimental work must be undertaken and many more patients will have to be treated early and effectively before any conclusions can be drawn in regard to the value of compression therapy in preventing invasion of the blood stream."

#### ABSTRACT OF DISCUSSION

DR ALFRED STENGEL, Philadelphia. When Friedman's report and later the more convincing paper of Coghlan appeared, it was hard for some physicians to believe that pneumonia could be treated safely and effectively by this method. They and the investigators who followed established that pneumothorax properly performed may be done in cases of lobar pneumonia with safety, and that circumstance may have led to some erroneous conceptions based on the earlier papers. The results that were obtained, for example, in Coghlan's work were too good to be believed, and it seems probable that some earlier results in cases of pneumonia which had advanced beyond the stage of the first day or two probably represented spontaneous recovery of persons who were not unfavorably influenced by the pneumothorax but who would have recovered without it. Unless this

treatment is used very early in the disease, the chances of its doing definite good are not great. On the other hand, I cannot believe that pneumothorax does not do something fundamental and radical in a case of early pneumonia. The authors rejected the theory that there is speeding up of the formation of antibodies by pneumothorax, and the explanation must be sought elsewhere. I believe that for the elucidation of these points this investigation must be pursued in the future by experimentation with animals. Much may be added by the trial and error method in further clinical studies, but to obtain a real solution of the mechanism that operates here a well thought out and rather extended series of investigations of many factors that might conceivably enter into the subject will be required. This treatment is not yet on an established basis, and members of the medical profession should not assume that because certain persons occasionally have obtained brilliant results, it is an operation to be performed by those who know little more about the details than that pneumothorax has been performed and the patients have recovered. The selection of cases, the training in the production of pneumothorax and a great many other factors enter into the problem. I think that it would be unfortunate if this treatment should be accepted now as being established for pneumonia and practiced widely. Much more work must be done before it can be accepted for use as a routine.

DR JESSE G M BULLOWA, New York. Since the publication of Coghlan's paper I have applied pneumothorax in the treatment of pneumonia in forty-two cases, in thirty-one before the seventy-second hour. The extent of pneumothorax was controlled by repeated roentgenograms. In my experience I have encountered little from which to infer that pneumothorax, even when applied on the first day of the illness, has beneficially influenced the progress of the disease, and some things have led me to believe that the reduction of the area of aeration may be definitely detrimental and may add the disadvantages of anoxemia to the toxemia and the possible bacteremia. I have observed an extension of the lesion in the lobe that was involved and the spread to another lobe on the side of the collapse in a patient suffering from pneumonia due to the type VIII pneumococcus treated on the third day. The lower lobe was involved and had been collapsed. The temperature decreased slightly, and on the sixth day the upper lobe of the left lung, though collapsed, became involved, and the temperature increased. The contralateral side became involved in three cases, as illustrated by a case of pneumonia due to the type V pneumococcus, in which pneumothorax was produced at the nineteenth hour for involvement of the lower lobe of the left lung. Good collapse occurred, but there was no favorable influence on the temperature and pulse from the repeated introduction of large amounts of air. The heart became displaced to the right. On the second day the blood culture became positive. Extension to the lower lobe of the right lung was found by a roentgenogram taken at the thirty-fifth hour. The patient then had to have air removed from the left side because of respiratory distress. He became delirious. On the fourth day administration of type V antiserum was begun, and he was placed in the oxygen chamber. He required 1,000,000 units. If he had been treated with serum on the first or second day, he would have required only several hundred thousand units. He recovered. In five cases the blood was invaded during treatment. There has not been dramatic relief from pain in any case. Delirium has been more frequent than usual in cases of pneumonia due to the type I pneumococcus. The problem of pneumonia is the bacteremia. If there is no bacteremia it is amazing how much a patient will stand and yet recover. With reference to the eighteen patients with pneumonia due to the type I pneumo-

coccus, six of whom died of bacteremia, I have had two hundred and thirty-nine patients with pneumonia due to the type I pneumococcus treated on the fourth and fifth days with specific serum but not with pneumothorax, thirty-three patients died, or 13.9 per cent. This treatment is not one for general practitioners or for those who have little experience with pneumonia or few facilities for treatment. Of one hundred cases of seven types of pneumococcic pneumonia, in which no specific treatment was given, in some the disease terminated on the first or second day. In many cases pneumonia due to the type I pneumococcus terminated on the fifth, sixth or seventh day. In most cases the condition terminated between the fourth and the twelfth day. The curve for each type was somewhat different from that of the others. Until the appearance of such a chart is changed by the use of a treatment for pneumonia, that treatment cannot be said to be beneficial.

DR FRANCIS G. BLAKE, New Haven, Conn. My associates and I have made a considerable number of studies on the mechanism involved. We have found no evidence of accelerated production of antibodies or evidence in support of the view advanced by Holmes and Randolph that the production of pneumothorax induces crisis by expelling exudate from occluded bronchi. We have been able to demonstrate by fluoroscopic study in a considerable number of cases that there is complete immobilization of the inflamed lung so far as respiratory movement is concerned. It is our opinion that this is probably the mechanism by which artificial pneumothorax exerts its effects. The eighteen cases of pneumonia due to the type I pneumococcus in our series, in six of which the outcome was fatal, were those of a late stage or of adhesions, and type I serum also was given in three cases. In our experience, as already stated, the treatment of pneumonia after the third day with artificial pneumothorax accomplished nothing in the way of cure. I agree with Dr. Stengel that it is too soon to use the method widely, because all the conditions under which it is or is not beneficial are not yet known.

## RELATIONSHIP OF FELTY'S AND ALLIED SYNDROMES TO SEPSIS LENTA

HARRY A SINGER, M D

AND

HERMAN A LEVY, M D

CHICAGO

In 1924, Felty<sup>1</sup> described the occurrence in five middle-aged adults of a syndrome characterized by chronic deforming arthritis, splenomegaly, lymphadenopathy, leukopenia and cutaneous pigmentation. Secondary anemia was present in all but one case, and in two patients low grade fever was detected. Felty apparently assumed that the clinical picture he had described had hitherto been unobserved in adults and offered two explanations for this unusual syndrome, namely, that the manifestations are part of one pathologic process, the counterpart in the adult of Still's disease of childhood, and that the syndrome is merely the confusion of two separate clinical entities, i e, chronic arthritis and Banti's disease, occurring coincidentally in the same person. Felty favored the former explanation chiefly on the basis of the law of probability and concluded that he was dealing with a distinct clinical entity caused by a "noxa which simultaneously affects the joints, spleen and blood leukocytes and in 3 of 5 cases the lymph nodes." No reference to Felty's article appeared in American literature for eight years, at the end of which time Hanrahan and Miller<sup>2</sup> recorded the case of a woman of 50, in whom chronic arthritis, splenomegaly, anemia, leukopenia and marked loss of weight were noted. Nodules, which were dusky red and painful, also were observed. A blood culture proved sterile. Hanrahan and Miller, who considered their case an example of Felty's syndrome, felt "that the marked splenomegaly and leucopenia were in themselves sufficient indication to warrant the operation (splenectomy) regardless of a possible favorable effect on the arthritis." Following the removal of the spleen the patient felt better generally and the arthritis improved greatly. The number of white cells increased from a count which varied between 640 and 1,600 before operation to 12,000 after operation. Culture of the splenic tissue proved sterile. Micro-

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From the College of Medicine, the University of Illinois and the departments of medicine and of pathology, Cook County Hospital

1 Felty, A R. Chronic Arthritis in the Adult, Associated with Splenomegaly and Leukopenia. A Report of Five Cases of an Unusual Clinical Syndrome, *Bull Johns Hopkins Hosp* **35** 16 (Jan) 1924

2 Hanrahan, E M, Jr, and Miller, S R. Effect of Splenectomy in Felty's Syndrome, *J A M A* **99** 1247 (Oct 8) 1932

scopically, swelling of the lining endothelial cells, erythrophagocytosis and infiltration of the pulp by plasma cells were noted. The question of the nature of the underlying disease process was left sub judice.

During the latter part of 1933 and the early part of 1934 three American publications dealing with Felty's syndrome appeared in medical literature. The first article, by one of us (H. A. S.),<sup>3</sup> was merely a summary of a brief paper given before the Central Society for Clinical Research on Oct. 28, 1933. The second article, which was written by Craven<sup>4</sup> and which appeared in March 1934, contained an account of a man who presented all five cardinal features of Felty's syndrome and in addition a subfebrile temperature. Splenectomy afforded only transient benefit. Sections of the spleen exhibited changes similar to those described by Hanrahan and Miller. Culture of an excised superficial lymph node yielded a green-producing streptococcus. Craven did not discuss the subject of etiology of Felty's syndrome and made no comment regarding the possible significance of the positive bacteriologic observation. More recently (April 1934) Price and Schoenfeld<sup>5</sup> described the case of a man 59 years old, who suffered from recurrent arthritis, splenomegaly and leukopenia. The arthritis was not apparently of the deforming type, and pigmentation and lymphadenopathy were lacking. Signs of fibrinous pleurisy were followed two weeks later by a pericardial friction rub, which disappeared after several days. The rub recurred ten days later, and on the night of its reappearance, just preceding the day on which splenectomy was to be performed, the patient died. The microscopic changes in the spleen consisted of "diffuse fibrosis with dilatation of the splenic sinuses. The latter showed areas of myeloid activity, with numerous plasma cells and eosinophils and an occasional bone marrow giant cell. There was diffuse, chronic septic splenitis." Price and Schoenfeld concluded that the case clinically was one of Felty's syndrome. They were led to believe that the splenomegaly of Felty's syndrome belonged to the same group of splenic diseases described by Giffin<sup>6</sup> and by Ward<sup>7</sup> owing to a variety of etiologic (infectious) factors.

Until the appearance of the brief communication by one of us (H. A. S.),<sup>3</sup> which appeared in December 1933, the association of deforming

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3 Singer, H. A. The Etiology of Felty's and Related Syndromes, *J. A. M. A.* **101** 2078 (Dec. 23) 1933.

4 Craven, E. B., Jr. Splenectomy in Chronic Arthritis, Associated with Splenomegaly and Leukopenia (Felty's Syndrome), *J. A. M. A.* **102** 823 (March 17) 1934.

5 Price, A. E., and Schoenfeld, J. B. Felty's Syndrome. Report of Case with Complete Post-Mortem Findings, *Ann. Int. Med.* **7** 1230 (April) 1934.

6 Giffin, quoted by Price and Schoenfeld.<sup>5</sup>

7 Ward, quoted by Price and Schoenfeld.<sup>5</sup>

arthritis, splenomegaly and lymphadenopathy in adults was considered, so far as recent American literature is concerned, unique. Thus Felty looked on the syndrome he described as a new entity, the counterpart of Still's disease in the adult. Hanrahan and Miller<sup>2</sup> apparently considered Felty to be the first to call attention to the syndrome to which they prefixed Felty's name. In the article by Craven<sup>4</sup> published in March 1934, reference is made to the treatises of Felty and Hanrahan and Miller, followed by the statement, "In the voluminous literature dealing with chronic arthritis, splenomegaly and leukopenia as separate entities, the simultaneous occurrence of the three abnormalities is not mentioned except in these two papers." Price and Schoenfeld,<sup>5</sup> whose article appeared in April 1934, attempted to show that the association of arthritis, splenomegaly and leukopenia is not as rare as it is considered by other American writers, but they failed to take cognizance of or to refer to the extensive foreign and older domestic literature which is to be summarized here.

Before a medical group, Still<sup>8</sup> in 1896 described a specific form of chronic joint disease in children since known by his name. The twelve distinctive cases which he separated from a group of twenty-two instances of chronic arthritis in children were characterized by "chronic, progressive enlargement of joints, associated with general enlargement of glands and spleen." A tendency to moderate anemia and arrest of physical development were noted, and in four cases there was undue prominence of the eyes. The most striking features in this form of juvenile chronic arthritis, viz., the involvement of the lymphatic glands and the enlargement of the spleen, were not found, as far as Still knew, in the adult. In three cases autopsy was performed, and in addition to the presence of a firm, enlarged spleen an adherent pericardium was found in all three. Still mentioned that the etiology was uncertain. Earlier in the year in which Still described the disease in children now known by his name, Chauffard and Ramond<sup>9</sup> reported the association of *adénopathies sus-articulaires* with chronic infectious arthritis in seven adults. Enlargement of the spleen was absent or at least not mentioned. The arthritis, which was quite different from the senile type, was characterized by paroxysmal febrile periods alternating with periods of remission, and the adenopathy was noted especially in the region of the affected joints. In two cases evidence of cardiac lesions existed. None of the cases were followed to autopsy. Chauffard and Ramond concluded that the adenopathy was secondary to the arthropathy, both lesions developing from the same infectious source. After a

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8 Still, G. F. On a Form of Chronic Joint Disease in Children, *Med-Chir Tr*, London **80** 47, 1896-1897.

9 Chauffard, A., and Ramond, F. Des adénopathies dans le rhumatisme chronique infectieux, *Rev de med*, Paris **16** 345 (May) 1896.

great deal of bacteriologic work with lymph glands and articular fluid a diplococcus was finally isolated from material taken from one patient

Since the time of Still<sup>8</sup> and of Chauffard and Ramond,<sup>9</sup> a rather voluminous literature has appeared dealing with the presence in both children and adults of chronic arthritis associated with either adenopathy or splenomegaly or both and variably with leukopenia, pigmentation, secondary anemia and subcutaneous nodules Bannatyne and Wohlman<sup>10</sup> in 1896 pointed out that rheumatoid arthritis commences as a progressive arthritis, deforming in nature, and later anemia, enlarged glands (especially in children) and such trophic disorders of the skin as pigmentation occur Delcourt<sup>11</sup> in 1898 described a case of chronic arthritis of the Still type in a 4 year old child, with autopsy In 1904, McCrae,<sup>12</sup> in reporting one hundred and ten cases of arthritis deformans from the service of Professor Osler at Johns Hopkins University, noted a general adenopathy in thirteen, enlargement of the spleen in four, marked pigmentation in eight and a leukocyte count of 5,000 or less in six cases Two examples of Still's malady were included Weber<sup>13</sup> described two cases of Still's disease in 1905 and referred also to the malady of a 16 year old girl with a rheumatoid condition and a palpable spleen as "probably a variety of Still's type occurring in an older patient" Von Jaksch<sup>14</sup> early in the twentieth century reported the occurrence in a 45 year old patient of chronic arthritis, a huge spleen, anemia and leukopenia, all of which he explained on the basis of a "gouty diathesis" A report of the autopsy was included Additional reports on Still's disease proper multiplied by such leaps and bounds that by 1914 Ibrahim<sup>15</sup> had succeeded in collecting from the world literature two hundred and seventy-three cases, to which he added six of his own

The first mention of the term Still-Chauffard's disease, used by European authors as corresponding to Felty's syndrome, was made by Pollitzer,<sup>16</sup> who in 1914 described two adult patients with chronic

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10 Bannatyne, G A, and Wohlman, A S Rheumatoid Arthritis Its Clinical History, Etiology and Treatment, *Lancet* **1** 1120 (April 25) 1896

11 Delcourt, A Rhumatisme articulaire nouveau chez les enfants, *Rev mens d mal de l'enf* **16** 329, 1898

12 McCrae, T Arthritis Deformans The Report of One Hundred and Ten Cases from the Johns Hopkins Hospital, *J A M A* **42** 1 (Jan 2) 1904

13 Weber, F P Still's Type of Chronic Joint Disease in Children and the So-Called "Tuberculous Rheumatism," *Brit J Child Dis* **2** 208, 1905

14 von Jaksch, A Arthritis urica, Megalosplenie und Leukopenie, *Deutsche med Wchnschr* **34** 634, 1908

15 Ibrahim, J Die chronische Arthritis im Kindesalter, *Ztschr f orthop Chir* **34** 213, 1914

16 Pollitzer, H Ueber chronischen Gelenkrheumatismus mit Drusenschwellung und Milztumor (Typus Still-Chauffard), *Med Klin* **10** 1511 (Sept 27) 1914



arthritis, enlarged lymph nodes and splenic tumor of "typus Still-Chauffard" In subsequent reports by continental writers dealing with the Still syndrome, the adult form (Still-Chauffard's disease) was sharply separated from the juvenile type The number of cases recorded in adults indicates that the disease is not nearly as rare or as new as suggested in American literature Schmidt<sup>17</sup> in 1917 recorded a case of *Still-Chauffardscher Erkrankung* occurring in a 40 year old white man afflicted with chronic generalized arthritis, universal adenopathy and enlargement of the spleen Bacteriologic studies of blood, fluid from the joints and excised nodes, both smears and cultures, gave uniformly negative results Goldstein<sup>18</sup> described a woman 38 years old with a typical Still-Chauffard syndrome, including marked leukopenia, with a white cell count of from 900 to 1,600, but lacking pigmentation A culture of the blood gave negative results In Herman's<sup>19</sup> case a 27 year old patient had deforming arthritis and enlarged nodes and spleen Vinkuroff and Levi<sup>20</sup> reported two cases, and because of negative bacteriologic observations they concluded that the exciting agent of this form of chronic arthritis is as yet undiscovered Steinitz and Casperfurstenheim<sup>21</sup> related the case of a 31 year old patient with a Still-Chauffard syndrome, including autopsy Chevallier<sup>22</sup> gave a complete and comprehensive discussion of various aspects of the Still-Chauffard and related syndromes and was the first to suggest removal of the spleen with the idea of inducing retrogression of the arthropathy Chevallier and Heuyer<sup>23</sup> reported a case illustrating a mild variety of Still-Chauffard's disease Weissenbach and others<sup>24</sup> reported several

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17 Schmidt, R Ein Fall von Still-Chauffardscher Erkrankung, *Med Klin* **13** 1076 (Oct 7) 1917

18 Goldstein, W Stillsches Krankheitsbild beim Erwachsenen, *Med Klin* **22** 1527 (Oct 1) 1926

19 Herman, K Ueber Still-Disease, *Klin Wchnschr* **6** 1807 (Sept 17) 1927

20 Vinkuroff, I Y, and Levi, G S Rare Clinical Cases of Chronic Diseases of Joints (Still-Chauffard Disease), *Odesskii med zhur* **3** 575 (Oct 28) 1928

21 Steinitz, H, and Casperfurstenheim, A Abortivform von Stillscher Krankheit mit Sclerodermie, *Med Klin* **26** 700 (May 9) 1930

22 Chevallier, P La maladie de Chauffard-Still et les syndromes voisins, *Rev de med, Paris* **47** 77 (Feb) 1930

23 Chevallier, P, and Heuyer, G Syndrome rhumatismal et adenopathique atteignant les membres inferieurs et evoluant par poussees qui guerissent (forme inferieure et atteneue de la maladie de Chauffard-Still), *Bull et mém Soc med d hôp de Paris* **54** 65 (Jan) 1930

24 Weissenbach, R J, Françon, F, Gerbay, F, and Robert, P Deux cas de syndrome de Chauffard-Still, *Bull et mém Soc med d hôp de Paris* **55** 172 (Jan) 1931

cases, and in a later article Weissenbach and Françon<sup>25</sup> presented an excellent general resume of the subject. A 40 year old patient with Still-Chauffard's disease was described by Lemierre and Mahoudeau-Campoyer,<sup>26</sup> who employed and recommended the intravenous injection of sodium salicylate. Etienne and others,<sup>27</sup> Saad,<sup>28</sup> Frugoni,<sup>29</sup> Costa<sup>30</sup> and Fieschi,<sup>31</sup> each reported one case, the last author recording pathologic observations. Giordano<sup>32</sup> presented ten case reports with a thorough review of the subject. Articles by Kramsztyk,<sup>33</sup> Micheli<sup>34</sup> and Ocaranza<sup>35</sup> probably included case reports but were not available to us. Rather recently (1933) Moltke<sup>36</sup> attempted to establish the similarity between Still's disease and the condition observed in his four cases of subchronic or chronic polyarthritis in young men with subfebrile temperature, polyadenitis and a disturbance of the general condition. Graber-Duvernay<sup>37</sup> described recently what he termed the Still-Chauffard syndrome occurring in six adults in all of whom adenopathy of the satellite type occurred but in only two of whom splenomegaly was present.

Of prime importance in connection with the subject of Still's disease and related syndromes is the etiology. Is there merely one cause or are

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25 Weissenbach, R. J., and Françon, F. Le syndrome de Chauffard-Still. Rhumatisme chronique fibreux déformant progressif avec adenopathies et splénomégalie. Sa place en nosologie, *Presse med* **39** 1197 (Aug 12) 1931.

26 Lemierre, A., and Mahoudeau-Campoyer, D. Efficacité des injections intraveineuses de salicylate de soude dans un cas de maladie de Chauffard-Still, *Gaz d hôp* **105** 1029 (July 9) 1932.

27 Etienne, G., Drouet, P. L., Touyot, P., and Richon, J. Un cas de maladie Chauffard-Still, *Bull et mém Soc med d hôp de Paris* **56** 1398 (Nov 4) 1932.

28 Saad, B. Un cas de maladie de Chauffard-Still, *Bull Soc franç de dermat et syph* **39** 757 (June) 1932.

29 Frugoni, C. Morbo di Still-Chauffard, *Policlinico (sez prat)* **39** 1077 (July 11) 1932.

30 Costa, A. Un caso di sindrome di Still, *Arch per le sc med* **56** 161 (March) 1932.

31 Fieschi, A. Poliartrropatia subacuta tipo Still-Chauffard, *Riforma med* **48** 511 (April 2) 1932.

32 Giordano, C. Contributo allo studio del morbo di Still-Chauffard, *Arch per le sc med* **55** 319 (July) 1931.

33 Kramsztyk, J. Gelenkrheumatismus mit Lymphdrusenschwellung (Still-Chauffard), *Pedjatrja polska* **2** 2, 1922.

34 Micheli, F. Sur la maladie de Still-Chauffard, *Acta rheumatol* **3** 11 (Feb) 1931.

35 Ocaranza, F. A propósito de un caso de enfermedad frustrada de Chauffard-Still, *Medicina, Mexico* **12** 417 (Aug 25) 1932.

36 Moltke, O. Still's Disease in Adults, *Ugesk f læger* **95** 737 (June 29) 1933.

37 Graber-Duvernay, J. Six observations de syndrome de Chauffard-Still chez l'adulte, *Acta med Scandinav* **81** 63, 1934.

there several different causes of the symptom complex under discussion? The micro-organisms which have been suspected include those of tuberculosis, syphilis and chronic low grade sepsis. These infections will be dealt with later. Other factors which have an etiologic bearing have been suggested. For instance, a possible endocrine element has been emphasized by some authors because of the associated exophthalmos, slight in the cases of Still,<sup>8</sup> Pollitzer<sup>16</sup> and Graber-Duvernay<sup>37</sup> and more marked in those of Koeppe,<sup>38</sup> Reimold and Stoeber<sup>39</sup> and Weissenbach and his associates<sup>24</sup>. In the last instance an actual hyperthyroidism, with a basal metabolic rate of plus 44 per cent was found. Vinkuroff and Levi<sup>20</sup> mentioned the thyrogenic arthritis of Veljaminov as a possibility but not a probability. The association of scleroderma was noted by Stoltzner,<sup>40</sup> Strauss,<sup>41</sup> Stoye<sup>42</sup> and Steinitz and Casperfurstenheim<sup>21</sup>. Pollitzer<sup>16</sup> and later Bauer,<sup>43</sup> Schmidt,<sup>17</sup> Muncke<sup>44</sup> and Goldstein<sup>18</sup> attributed at least part of the peculiarities of these syndromes to the existence of a lymphatic constitution or predisposition. However, they, as well as most other investigators, stated the belief that an infection is the primary etiologic agent and that the lymphatic constitution accounts merely for the peculiar response on the part of the spleen and lymph nodes.

A tuberculous rheumatism, such as Poncet<sup>45</sup> described in 1901, in three frankly tuberculous patients with arthritic manifestations has been assumed by later authors to be present in Still's disease. The evidence for a Koch infection is not at all convincing, as a review of the reports pertaining to this phase of the subject will disclose. Edsall<sup>46</sup> cited a case of Still's disease on a tuberculous basis in a 13 year old boy in whom the injection of old tuberculin produced a definite rise in temperature and pains in the joints. Although no evidence of tuberculosis

38 Koeppe, H. Ein Fall von "Still'scher Krankheit," *Jahrb f Kinderh* **76** 707, 1912

39 Reimold, W., and Stoeber, T. Beitrage zum Problem der Stillschen Krankheit, *Monatschr f Kinderh* **31** 597 (March) 1926

40 Stoltzner. Stillsche Krankheit mit Sklerodermie, *Deutsche med Wchnschr* **50** 1136, 1924

41 Strauss, H. Ueber Stillsche Krankheit, *Med Klin* **22** 1247 (Aug 13) 1926

42 Stoye, W. Ein Beitrag zur Atiologie der Stillschen-Krankheit und der herdfornigen Sklerodermie, *Ztschr f Kinderh* **41** 538, 1926

43 Bauer, J. Die konstitutionelle Disposition zu inneren Krankheiten, Berlin, Julius Springer, 1917

44 Muncke, A. Ein Beitrag zur Pathologie der Stillschen Krankheit, *Med Klin* **20** 1502 (Oct 26) 1924

45 Poncet, A. Rhumatisme tuberculeux ou pseudo-rhumatisme d'origine bacillaire, *Gaz d hôp* **74** 817 (July 25) 1901

46 Edsall, D. L. Concerning the Nature of Still's Type of Chronic Polyarthritis in Childhood, *Arch Pediat* **21** 175, 1904

was obtained in a lymph node removed from the axilla, in an emulsion of several nodes a large number of acid-fast organisms considered to be typical Koch bacilli were found. However, the injection of this same emulsion into guinea-pigs resulted in no change in the health of the animals, and after five weeks no evidence of tuberculosis was detected in the internal organs. The only evidence that Weber<sup>13</sup> had for diagnosing the condition in his second case as tuberculous rheumatism was the production of a general reaction, including a temperature of 101 F., by the injection of old tuberculin used for the Pirquet test. No local reaction occurred. One of Piske's<sup>47</sup> patients, an 8 year old girl with polyarthritis, enlarged nodes and spleen, definite involvement of the lungs and a negative Pirquet reaction and culture of the blood, was found at autopsy to have miliary tubercles in various organs, including the spleen. However, the superficial nodes were not involved. Piske concluded that he was dealing with Poncet's type of tuberculous rheumatism. Cozzolino<sup>48</sup> in 1914 assumed tuberculosis to be the cause of an arthritis and adenitis in a 7 year old patient on the basis solely of a positive reaction to tuberculin. For the etiologic agent of two cases of Still's malady, Longo<sup>49</sup> mentioned tuberculosis as a good possibility but included no evidence in favor of it, for in both instances the reaction to tuberculin was negative and neither patient came to autopsy. With regard to syphilis, there is even less evidence for the assumption that it causes Still's disease or related syndromes. The only case in which an etiology of syphilis might be entertained is that reported by Weissenbach and Françon<sup>25</sup>. These authors reported the case of a 15 year old girl with hereditary syphilis in whom a Still-Chauffard syndrome and certain thyro-ovarian disturbances retrogressed under anti-syphilitic and endocrine treatment.

Since Chauffard and Ramond<sup>9</sup> in 1896 searched diligently but unsuccessfully for the causative organism, a great deal of bacteriologic work has been performed in an attempt to find the specific etiologic factor. Piske<sup>47</sup> made cultures of blood in a search for streptococci or staphylococci but failed to recover any. Pisek,<sup>50</sup> an American author, stated "The polyarthritis described by Still seems to be the result of a chronic sepsis, which while not sufficiently potent to completely overpower the young organism, has destroyed resistance by enfeebling the

47 Piske, J. Zur Kenntnis der Stillschen Krankheit, *Med. Klin.* **9** 1968 (Nov. 30) 1913.

48 Cozzolino, O. Un caso di reumatismo articolare cronico tubercoloso in bambina (con la sintomatologia del morbo di Still), *Pediatria* **21** 401, 1913.

49 Longo, A. Contributo allo studio della così detta malattia di Still, *Riv. di clin. pediat.* **15** 225, 1917.

50 Pisek, G. R. The Present Status of Still's Disease, *Arch. Diagnosis* **2** 355, 1909.

phagocytic power of the blood and lowering the activity of the lymphatics" His cultures of material aspirated from the joints, however, remained sterile Westmeyer<sup>51</sup> suspected chronic sepsis because of recurrent chills and fever, but two cultures of the blood gave negative results Litchfield<sup>52</sup> in 1922 stated "Despite the absence of demonstrable bacterial causation (negative blood culture), the assumption of a continual or recurrent bacteremia of low-grade with joint deposition seems plausible" Iseke,<sup>53</sup> by making cultures of material removed post mortem from the spleen, lungs, endocardium and middle ear of a 2 year old child with Still's syndrome, was able to obtain *Streptococcus viridans* in almost pure form He concluded that a chronic sepsis possibly of an endocarditis lenta type was the cause of Still's disease The next year Johansson,<sup>54</sup> in reporting a case, concluded that Still's disease is the expression of a chronic sepsis Strauss<sup>41</sup> in 1926, in spite of negative results from cultures of blood removed post mortem and negative bacteriologic results from cultures of tissue, joints and nodes, considered the disease a "lenteszierender" streptococcic sepsis, in which there is a peculiar type of mesenchymal reaction on the part of the spleen, lymph nodes, pericardium and pleura

The first investigators to recover the probable etiologic agent from the blood stream during life were Reimold and Stoeber<sup>39</sup> After repeated failures they finally succeeded in culturing from the circulating blood of a child with Still's disease a pure growth of *Str viridans* Stoye<sup>42</sup> found nonhemolytic (indifferent) streptococci in the blood of the heart of a patient with Still's disease, who, however, died of bronchopneumonia Debre and others<sup>55</sup> described a boy of 10 years with a typical Still complex associated with endocarditis of the lenta type Although cultures of the blood gave negative results, the authors concluded that the entire picture was the result of sepsis due to *Str viridans* In support of their contention they referred to an observation of an absolutely characteristic endocarditis lenta, verified by the finding of *Str viridans* in the circulating blood, occurring in an adult with chronic deforming arthritis Recently Bennholdt-Thomsen<sup>56</sup> recorded the recovery of

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51 Westmeyer, J Der chronische Gelenkrheumatismus im Kindesalter, *Jahrb f Kinderh* **81** 69, 1915

52 Litchfield, H R Still's Disease (Atrophic Arthritis), *Arch Pediat* **39** 107, 1922

53 Iseke, G Zur Aetiologie der Stillschen Krankheit, *Ztschr f Kinderh* **35** 315 (June) 1923

54 Johansson, N Ein Beitrag zur Kenntnis der "Still'schen Krankheit," *Acta paediat* **2** 354, 1924

55 Debre, R, Broca, R, and Lamy, M Forme endocardique de la maladie de Still, *Arch de med d enf* **33** 212 (April) 1930

56 Bennholdt-Thomsen, C Zur Stillschen Krankheit, *Klin Wchnschr* **13** 236 (Feb 10) 1934

*Staphylococcus aureus* four times and of *Str. viridans* once from the blood of a 2½ year old child with Still's disease. He viewed the syndrome as a slowly developing form of sepsis of the lenta type, the infectious agent being *Str. viridans*. As to whether *Staph. aureus* plays an accompanying rôle must be determined, he thought, by further investigation. The data in connection with two adult patients we have studied lend support to the view that Felty's syndrome is the result of a low grade sepsis, probably streptococcic. The evidence pointing to a chronic sepsis of the lenta type is not limited to the bacteriologic results but includes also the anatomic observations. Case 1, although observed later than case 2, is presented first since the former offers a more typical picture of the condition from the standpoint of both clinical examination and necropsy.

#### REPORT OF CASES

CASE 1—I W., a white man 55 years of age, dated the onset of his malady back to 1924, when he acquired polyarthritis, affecting the joints of the hands, shoulders, knees and ankles. The involved joints were red, swollen, tender and painful. At the end of three months' confinement to bed, although not completely recovered, the patient was able to be up and about. Within the next four years, coinciding with exacerbations of arthritis, subcutaneous nodules appeared, varying in size from that of a pea to that of a walnut, which were situated near the affected joints. At first these nodules were tender, but later they became painless. During the period in which the subcutaneous nodules were prominent the patient attended a large clinic, where the diagnosis of secondary anemia and chronic infectious arthritis was made, although gout could not be ruled out. The patient's tonsils were removed, the teeth extracted and a chronic prostatic inflammation treated by various measures. Physical therapy was advised. The subsequent course of the arthritis was marked by remissions and exacerbations. In the meantime deformity of the hands developed. In 1931, the patient entered another hospital for observation. At this time, enlargement of the spleen and pigmented areas on the legs were noted in addition to the deforming arthritis. The examination of the blood revealed an erythrocyte count of 3,200,000, a hemoglobin content of 65 per cent and a leukocyte count varying from 2,400 to 8,700, with an average of 5,100 for seven determinations. The differential count showed a marked preponderance of lymphocytes, varying from 58 to 80 per cent. A biopsy of an inguinal lymph gland was reported as showing the histologic picture of chronic lymphadenitis. The condition was diagnosed on discharge as aleukemic leukemia, with complicating chronic atrophic arthritis. Because of his disabling arthritis the patient was sent to the Oak Forest Infirmary, the home for incurable patients of Cook County. The patient left Oak Forest to enter the Cook County Hospital on Nov. 9, 1932.

On entrance the patient was moderately undernourished and not acutely ill. The temperature and the pulse and respiratory rates were normal. The heart was not enlarged, and no abnormal sounds were heard. The blood pressure was 130 systolic and 70 diastolic. The liver, which was palpable 6 cm. below the costal border, was not tender. The spleen was firm, smooth and greatly enlarged, reaching below the umbilicus and projecting above the level of the remainder of the abdomen (figs. 1 and 2). Enlarged lymph nodes were noted in the cervical, axillary, epitrochlear and inguinal regions. Deforming arthritic changes were

present in the joints of both hands, the fingers being fixed in flexion at the metacarpophalangeal joints. Located at the left elbow, right knee and right inguinal regions were old surgical scars, the sites from which specimens were taken for biopsy. The skin had a generalized light tan muddy discoloration, with numerous well demarcated patches of dark brown pigmentation of variable size located on the lower extremities. There was bilateral hallux valgus. Examination of the blood yielded an erythrocyte count of 3,450,000, a hemoglobin content of 63 per cent, a leukocyte count which varied from 950 to 1,500, and a differential count



Fig 1 (case 1) —Photograph of an adult with Felty's syndrome, illustrating arthritis deformans of the hands, splenomegaly (indicated by prominence of the abdomen, fig 2) and patchy pigmentation of the lower extremities. The lymphadenopathy is not sufficiently marked to be discerned. The white blood count ranged from 950 to 1,500 per cubic millimeter.

of 24 per cent polymorphonuclears, 72 per cent lymphocytes and 4 per cent monocytes. A splenic puncture revealed the presence of the following cells in the aspirated material, polymorphonuclear leukocytes 2 per cent, eosinophils 1 per cent, lymphocytes 95 per cent and monocytes 2 per cent. The lymphocytes, which measured up to 16 microns in diameter, had coarsely trabeculated nuclei

and homogeneous basophilic cytoplasm. Many basket cells, numerous polychromatophilic erythrocytes and an occasional normoblast were seen. Chemical studies of the blood afforded no noteworthy information. The Wassermann reaction of the blood was negative. A roentgenogram of the affected joints showed marked deformity but no bony changes. Roentgenograms of the lungs disclosed an area of calcification in the apex of the upper lobe of the left lung.

The presence of deforming arthritis, in association with splenomegaly, lymphadenopathy, leukopenia, secondary anemia and the peculiar form of pigmentation of the legs, led to the diagnosis of a Still-Chauffard or Felty syndrome. The investigation to determine if possible the underlying cause furnished evidence pointing to the existence of a sepsis lenta. For instance, a biopsy of an inguinal lymph node showed changes indicative of a chronic low grade infectious process, and a blood culture yielded a pure growth of *Str. viridans*. On the basis of the recent experience of Hanrahan and Miller, the advisability of splenectomy was considered and was mentioned to the patient. Since skepticism with regard to the ultimate benefit was expressed, the patient declined to take the risk. Treatment was practically entirely symptomatic. The subsequent course was char-

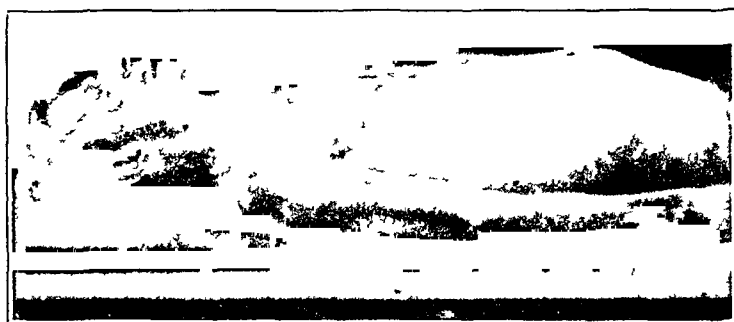


Fig 2 (case 1) —With the patient supine the enlarged spleen is seen to project above the level of the remainder of the abdomen

acterized by short periods of fever, a temperature generally subfebrile but occasionally reaching from 101 to 102 F, an increasing anemia, progressive weakness and repeated showers of petechial hemorrhages. The clinical resemblance to subacute bacterial endocarditis was very striking at this time. About six weeks before the patient's death, evidences of cardiac decompensation supervened. The patient became progressively weaker and died on April 25, 1933, six and one-half months after entrance to the hospital.

*Autopsy*—The macroscopic and histologic examinations were made by Dr R. H. Jaffe. The most informative changes were disclosed by microscopic examination.

*Macroscopic Examination* The salient changes observed post mortem can be briefly summarized as follows. Externally there was evidence of marked loss of weight and of anemia. In the skin of the upper eyelids were many purple-red petechiae, measuring up to 2 mm in diameter. Numerous similar hemorrhagic spots were seen in the skin of the lower extremities, where, in addition, irregular, discrete and confluent dark gray-brown areas with geographic outlines measuring as much as 5 cm in one dimension were found. The fingers were fixed in flexion with slight nodular deformities at the metacarpophalangeal articulations. The superficial lymph glands were enlarged, firm and discrete and measured up to 1.5 cm in diameter. There was an extreme hallux valgus involving both feet.



In the abdominal cavity was about 3,000 cc of a brownish cloudy fluid. In the omentum and mesentery were numerous recent petechial hemorrhages. The lower pole of the spleen extended 6 cm below the costal arch. The lower border of the liver was 13 cm below the xiphoid process and 7 cm below the costal arch. Both pleural cavities were obliterated by firm fibrous adhesions. The pericardial sac was obliterated by loose fibrous adhesions. The heart weighed 340 Gm. The left and right ventricular walls measured 15 and 3 mm, respectively. The myocardium was dark, brown-gray and friable. The valves of the heart were unchanged. The aorta and some of its main branches contained hyaline and fatty plaques. The left coronary artery presented similar changes and in addition calcified plaques. The lungs were subcrepitant and moist in portions. In the subapical region of the left lung was an indurated, deeply pigmented fibrosed area in which were several fibrocalcereous nodules, measuring up to 2 mm in diameter.

The spleen weighed 1,710 Gm and measured 10 by 18 by 30 cm. It was of firm consistency, and attached to its thickened capsule were numerous fibrous adhesions. Its sectioned surface was deep purple-red, mottled with lighter areas. The trabeculae and follicles were distinct, the latter light gray and the size of a pinhead. The liver, which weighed 1,930 Gm, was firm, smooth and purple-brown with the capsule thickened in places. The sectioned surface was brown-gray with purple-red acinar markings. The kidneys together weighed 310 Gm. Each kidney was moderately firm, the capsule stripped with ease, leaving a smooth surface which was purple-gray with many purple patches up to the size of a pinhead. The sectioned surface showed the cortex to be 4 mm thick, light purple-gray and studded with purple-red areas from the size of a pinhead to that of a pinpoint. The bone marrow was soft and a pale rust-brown.

**Microscopic Examination** Only those organs and structures in which significant changes were found are described.

In the spleen the endothelial cells lining the sinusoids were quite prominent, being swollen and increased in number. They exhibited a more marked cytoplasmic body and took an increased basophilic stain (fig 3). The sinusoids and cords were packed with red blood cells. Among the red cells in the sinusoids were desquamated endothelial cells. In the pulp were numerous plasma cells, often showing signs of degeneration (pyknosis of the nucleus), a moderate number of small and medium sized lymphocytes and a considerable number of free histiocytes with kidney-shaped nuclei and engulfed blood pigment. Single normoblasts and neutrophilic leukocytes with indistinct granulation and a few oxyphilic leukocytes were also found. The follicles were of medium size and lymphocytic, and the reticulum near the center often was hyalinized. In the trabeculae were elongated, flat, iron-containing cells.

The structure of the liver was somewhat irregular because of circumscribed areas of alteration of liver cells. Streaks of shrunken liver cells with pyknotic nuclei permeated the lobules and extended in different directions, often from the central vein toward the periportal tissue. In these areas capillaries were congested. Other areas of atrophy of the liver cells, which were more focal and marked by a proliferation of the Kupffer cells, were seen. Excluding these two types of circumscribed parenchymatous alteration, the liver cells were well preserved and occasionally contained large droplets of fat. Brownish pigment granules were found in many of the liver cells, especially near the central veins and in the areas of atrophy. Throughout the lobules the Kupffer cells were greatly swollen, with ample cytoplasm, and exhibited at times nuclei which were the shape of a

kidney bean (fig 4) In the sinusoids were single plasma cells and many free rounded histiocytic elements containing blood pigment The periportal tissue was infiltrated by lymphocytes and plasma cells

The sinuses of the abdominal lymph nodes (peripancreatic, peribiliary) were wide and lined by swollen endothelium and contained erythrocytes and proliferated endothelial cells, many of which contained red blood cells or blood pigment The secondary follicles were small, with histiocytic centers Groups of reticular cells filled with iron pigment were seen

Skin taken from the thigh showed a great deal of iron pigment in the cutis, enclosed in elongated, often spindle-shaped, cells Accumulations of these iron-containing cells were particularly evident about the sweat glands in the form of

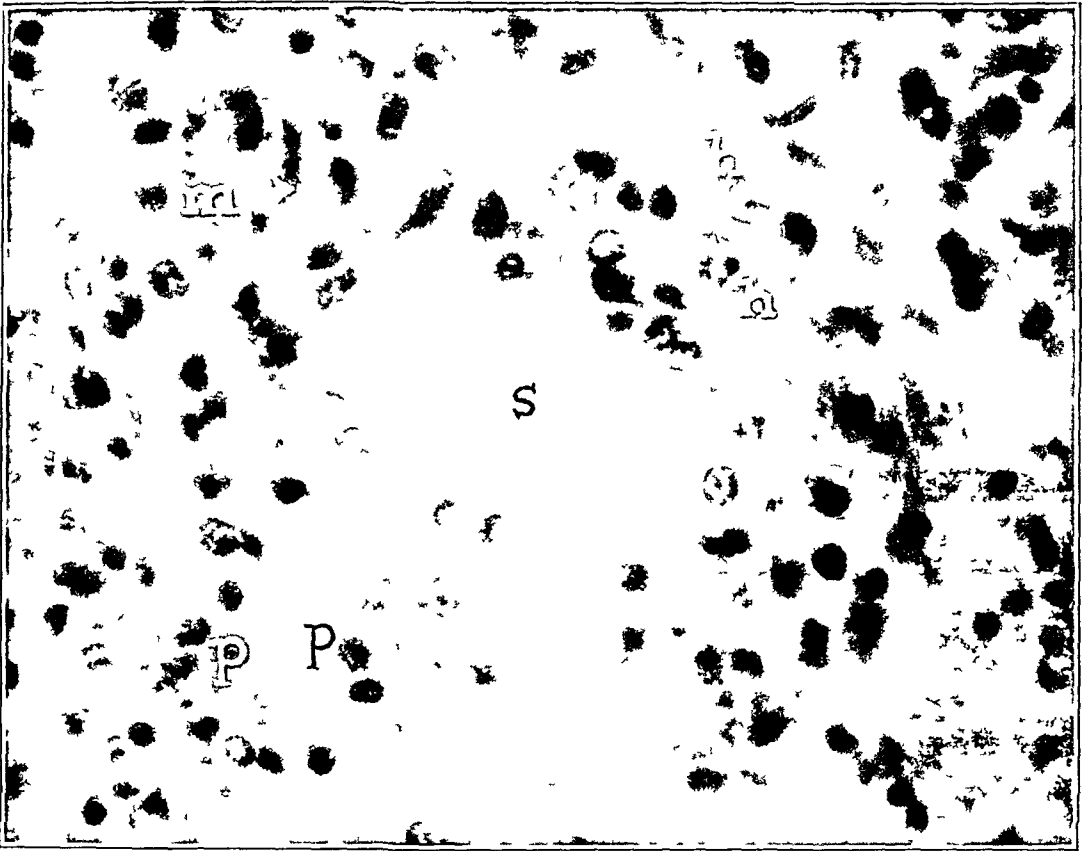


Fig 3 (case 1) —Photomicrograph of a frozen section of spleen stained with hematoxylin and eosin The lining of the splenic sinus (*s*) is unusually prominent, owing to swelling and increase in number of the endothelial cells Bordering the sinus is a large macrophage (*m*) with engulfed erythrocytes Other histiocytic cells (*h*) and plasma cells (*p*) are distributed throughout the pulp Magnification,  $\times 600$

heavy coats The adventitial cells of the cutaneous capillaries were engorged with iron granules also The melanin in the basal layer of the epidermis was not increased

Throughout the bone marrow there was marked congestion, and the fatty portions exhibited signs of atrophy and formation of a net of fibrin The reticulum was inconspicuous The endothelium of the blood vessels was somewhat prominent

The cellularity of the bone marrow was 37 per cent (the fat tissue representing the remaining 63 per cent) The neutrophilic myelocytes showed signs of severe alteration, intact granulation being completely absent In place of the normal granules there were found small, purple-pink, pale vacuoles having a tendency to fuse The nuclei of the myelocytes were round or bean-shaped, and the chromatin was broken up in coarse, round or angular granules which were linked by ill defined threads The nucleoli were difficult to differentiate from the chromatin granules However, the nuclear membranes were usually intact Some of the nuclei were shrunken and pyknotic An abortive mitosis was occasionally observed The sparse, mature neutrophils present revealed similar degenerative processes The oxyphilic granulocytes were much better preserved but occasionally showed

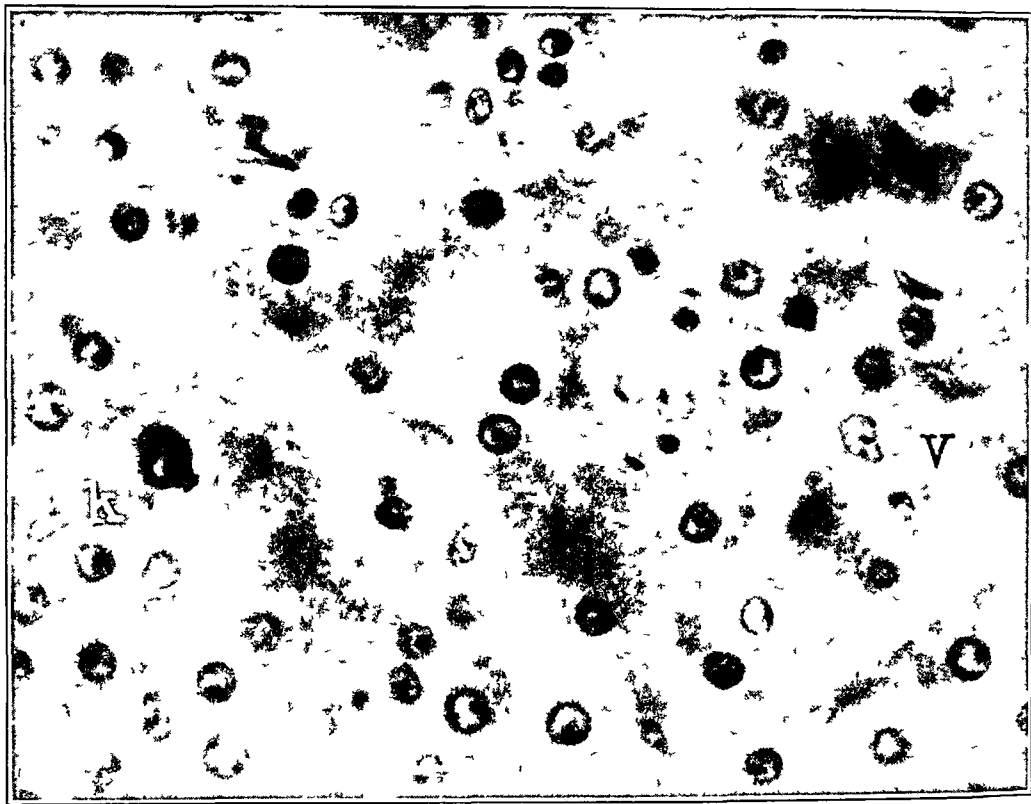


Fig 4 (case 2) —Section of the liver (frozen) stained with hematoxylin and eosin The Kupffer cells are conspicuous, chiefly because of swelling The cytoplasm is increased in amount and is at times vacuolated (*v*) Some of the nuclei are the shape of a kidney bean (*k*) Many round histiocytic elements lie free in the lumens of the sinusoids Magnification,  $\times 600$

transformation of granules into droplets The myeloblasts were intact The nucleated red cells varied considerably in size The majority of plasma cells were degenerated and had pyknotic nuclei The megakaryocytes were greatly altered their nuclei being shrunken and segmented and their granulation completely obscured The differential count was as follows myeloblasts 1 per cent, neutrophilic myelocytes 33.6 per cent, neutrophilic leukocytes 0.7 per cent, eosinophilic myelocytes 0.6 per cent, eosinophilic leukocytes 3.1 per cent, erythrogonia 2.8 per

cent, erythroblasts 127 per cent, normoblasts 366 per cent, lymphocytes 1 per cent, plasma cells 65 per cent, monocytoïd cells 1 per cent, and megakaryocytes 04 per cent

The connective tissue about the larger vessels of the heart was increased in amount, loose and edematous. It contained many swollen fibrocytes and loosely scattered lymphocytes and plasma cells. In the perivascular connective tissue were nodular accumulations of large cells with ample cytoplasm. Some of the nuclei of these cells showed the myocytic arrangement of the chromatin. Between these cells there was a varying number of small round cells, but no central area of fibrinoid necrosis was present. The muscle fibers were free from fat, and the cross-striations indistinct. There was considerable pigment at the poles of the nuclei. In the interstitial tissue were scattered, recent extravasations of blood.

The glomeruli of the kidneys were cellular, and the tufts often were plastered together and occasionally herniated in the openings of the tubules. Cells with oval or elongated nuclei predominated. The basal membrane was slightly thickened. Some of the glomeruli were completely, others partially, hyalinized. Here and there a crescent was observed in advanced fibrous transformation. Many of the convoluted tubules were filled by recent blood, others contained hemoglobin-tinted hyaline or waxy casts. A few glomeruli were associated with blood in Bowman's space. The tubular epithelium was often swollen and granular or contained hyaline droplets. An occasional tubule was lined by cells containing droplets of fat or iron granules. The stroma was slightly increased, especially about the hyalinized glomeruli. Some focal round cell infiltration was noted. The intima of the medium-sized arteries was moderately increased, whereas the walls of the arterioles were slightly thickened.

*Bacteriologic Studies*—A culture of material from the spleen yielded a pure growth of *Str. viridans*.

*Anatomic Diagnosis*—The diagnosis was sepsis lenta, huge tumor of the spleen with perisplenic adhesions, subacute glomerulonephritis, enlargement of the superficial and abdominal lymph nodes, petechial hemorrhages in the skin, peritoneum, kidneys, gastric mucosa and renal pelvis, irregular pigmentation of the skin of the lower extremities due to iron deposits in the cutis, ascites, brown atrophy of the heart, fibrous obliteration of the pericardial sac, fibrous obliteration of both pleural cavities, moderate passive congestion of the liver and lungs, fibro-calcareous subapical tuberculosis of the upper lobe of the left lung, focal broncho-pneumonia of the lower lobe of the left lung, moderate emaciation, arthritis deformans of the hands, bilateral hallux valgus.

**CASE 2**—A white woman aged 49 entered the Cook County Hospital for the first time on July 1, 1932, because of symptoms referable to an acute cardiac decompensation. She stated that for at least five years previously she had suffered from arthritic manifestations involving principally the joints of the hands and knees. A week before entrance, while arising, she experienced precordial tightness and dyspnea. Edema of the feet followed. The constricting sensation and dyspnea increased in severity, and on this account she entered the hospital. Aside from arthritis, there was nothing of significance in her past history, except perhaps that she had influenza in 1918. There was no family history of rheumatic fever. She had borne no children. On physical examination the patient was found to be dyspneic and cyanotic. The blood pressure was 170 systolic and 110 diastolic. A systolic murmur was heard over the apex, and a gallop rhythm was detected. The liver was felt to extend 2 fingerbreadths below the costal margin. Nothing was recorded with regard to the size of the spleen. Dependent edema was noted.

There was deforming arthritis of the hands, the fingers being fixed in flexion at the metacarpophalangeal joints

The patient rapidly improved under routine treatment for cardiac decompensation. During the early period of her confinement to bed, an irregular temperature was observed, frequently reaching 101 or 102 F and persisting at that level for a few days at a time. The patient was allowed to be up on July 22 and was discharged on July 26 feeling well. She was home for a few days, when on August 5 pain was felt in the region of the right ear. A purulent discharge appeared two days later, and on August 11 the manifestations of erysipelas developed on the right side of the face. On this account the patient reentered the hospital on August 12 and remained for five days, at the end of which time the erysipelas had disappeared.

The patient returned to the hospital in a critical state on October 24. She related that after her discharge in August she had several attacks of shortness of breath and fainting. She had suffered also from attacks of vomiting, presumably due to digitalis which had been taken intermittently. Pallor, which was now quite apparent, had been noted by the patient for several months. The loss of weight during this time was approximately 30 pounds (13 Kg). However, the patient was not confined to bed continuously until three days prior to the last admission, when a severe rigor occurred, followed by fever, sore throat and minor chills. Physical examination on admission disclosed an acutely ill white woman, very pale, dyspneic and toxic, with a temperature of 105.6 F, a pulse rate of 136 and a respiratory rate of 30. The skin and mucous membranes were tinted light yellow. Covering the tonsils and pharynx was a dirty yellowish-gray membrane which bled easily on manipulation. The anterior cervical lymph nodes were enlarged, especially on the right side. The heart was slightly enlarged to the left and over the apex a faint systolic blow was heard. The blood pressure was determined to be 170 systolic and 110 diastolic. Moist rales were heard over the bases of both lungs posteriorly, but no dulness could be demonstrated. The abdomen was tender in the left upper quadrant. The spleen was greatly enlarged to palpation. Deforming arthritis affecting the hands was also noted.

The initial diagnostic impression was agranulocytic anemia. Examination of the blood showed an erythrocyte count of 1,480,000, a hemoglobin content of 35 per cent and a leukocyte count of 450. The differential count was lymphocytes 81 per cent, monocytes 17 per cent, irritation forms 2 per cent and no granulocytes. No reticulocytes were encountered. The erythrocytes showed slight anisocytosis, poikilocytosis and an occasional polychromatophilic cell. A volumetric determination of the platelets showed 0.0006 per cent, equivalent to 42,000 platelets per cubic millimeter. The bleeding time was four and one-half minutes and the coagulation time eighteen minutes. Because of the depression of all the blood elements the diagnosis was revised to aplastic anemia. The presence of chills and fever suggested a septicemia as the cause of the aplastic blood picture. Blood which was drawn for culture revealed a pure growth of *Str. viridans*. Cultures of material from the throat and mucous membrane showed both *Str. viridans* and *Str. haemolyticus*. It was learned later that on Oct. 4, 1932, while the patient was under his care, Dr. H. C. Lueth obtained a pure growth of *Str. viridans* from the circulating blood. After frequent attacks of vomiting and a temperature varying from 104 to 106 F the patient died two days following entrance. Necropsy was performed shortly after death by Dr. R. H. Jaffe.

*Autopsy*—The salient features in the gross description can be briefly summarized. The microscopic changes in certain organs, however, require a detailed account.

**Macroscopic Examination** There were moderate emaciation, marked pallor of the skin and mucous membranes and slight icteric discoloration of the conjunctivae. The superficial cervical lymph glands were moderately enlarged. Over the pharynx and covering the tonsils were necrotizing membranous deposits, beneath which were relatively clean ulcers. The fingers of both hands were fixed in a flexed position, and the joints were deformed by nodular swellings about the articular surfaces. The inguinal lymph glands were moderately enlarged and discrete. The spleen, which measured 6 by 12 by 22 cm and weighed 620 Gm, extended 7 cm below the costal arch in the anterior axillary line. It was moderately firm in consistency, and when sectioned the surface was found to be moist and light purple-gray, with light gray follicles measuring up to 1 mm in diameter. On the posterior aspect near the upper pole there was a small, recent subcapsular anemic infarct. The liver weighed 1,950 Gm and was moderately firm, smooth and purple-brown. The sectioned surfaces showed the acinar markings to be irregular. The heart weighed 365 Gm. The myocardium was light purple-brown and friable, and the valves of the heart were macroscopically unchanged. The lungs were moderately distended and subcrepitant, containing recent extravasations of blood. The kidneys were swollen and soft, and on the sectioned surfaces the cortical markings were obscured. There was a moderate swelling of the periaortic and peripancreatic lymph nodes, which were soft and purple-gray, and measured up to 1 by 1.5 by 3.5 cm. The bone marrow of the femur was soft and a light purple-gray.

**Microscopic Examination** Only those organs or structures which demonstrated significant changes are included.

The sinuses of the spleen were wide and the lining endothelium only slightly prominent. The sinuses contained red blood cells, erythroblasts, normoblasts and a number of free histiocytes, each having a lobulated nucleus. The reticulum of the cords was markedly thickened, and its meshes contained small round cells, an increased number of plasma cells, a few nucleated red blood cells and an occasional megakaryocyte. The fibrillar hyperplasia was in striking contrast to the cellular hyperplasia of the reticulum as observed in case 1. The sinuses were sharply demarcated from the cords. The capsule and trabeculae were thickened. The lymph follicles were large and consisted only of lymphocytes. The reticular cells were slightly swollen. Underneath the capsule there was a wedge-shaped area which was completely necrotic and which was surrounded by a zone of marked congestion. Many of the sinuses in this region were filled by a dense net of fibrin.

The portal capillaries of the liver were diffusely dilated and filled by red blood cells, between which were clumps of platelets. There were moderate numbers of normoblasts and polychromatophilic erythroblasts. The Kupffer cells were prominent and possessed ample, occasionally vacuolated cytoplasm. Some of the Kupffer cells contained fat droplets. Free histiocytic elements, however, were relatively scanty. In the center and in the periphery of the acini, the liver cells contained small droplets of fat. The periportal tissue was densely infiltrated by lymphocytes, and between the lymphocytes were noted large mononuclear cells, the cytoplasm of which stained diffusely yellow.

The sinuses of the abdominal lymph nodes (periaortic and peripancreatic) were very much dilated and predominated over the lymphatic structures. The former were filled by erythrocytes and desquamated, large endothelial cells containing erythrocytes. The lymphatic tissue consisted of a mixture of lymphocytes, many plasma cells and a few large basophilic round cells. Secondary follicles were not visible. The reticular cells were markedly swollen.

The sinuses and capillaries of the bone marrow were dilated and congested. Most of the cellular elements were found outside the preformed blood spaces, in which only an occasional nucleated element could be detected. The reticular cells were swollen, and many of them contained engulfed red blood cells. The endothelium of the blood vessels was only moderately conspicuous. The cellularity of the bone marrow was 80 per cent, the fat tissue representing 20 per cent. The differential count gave the following figures and characteristics. There were 0.2 per cent myeloblasts and 2 per cent degenerated myelocytes. The myelocytic nucleus was usually fairly well preserved, but the cytoplasm appeared torn up or finely vacuolated. There was an occasional ill defined purple-pink granule or

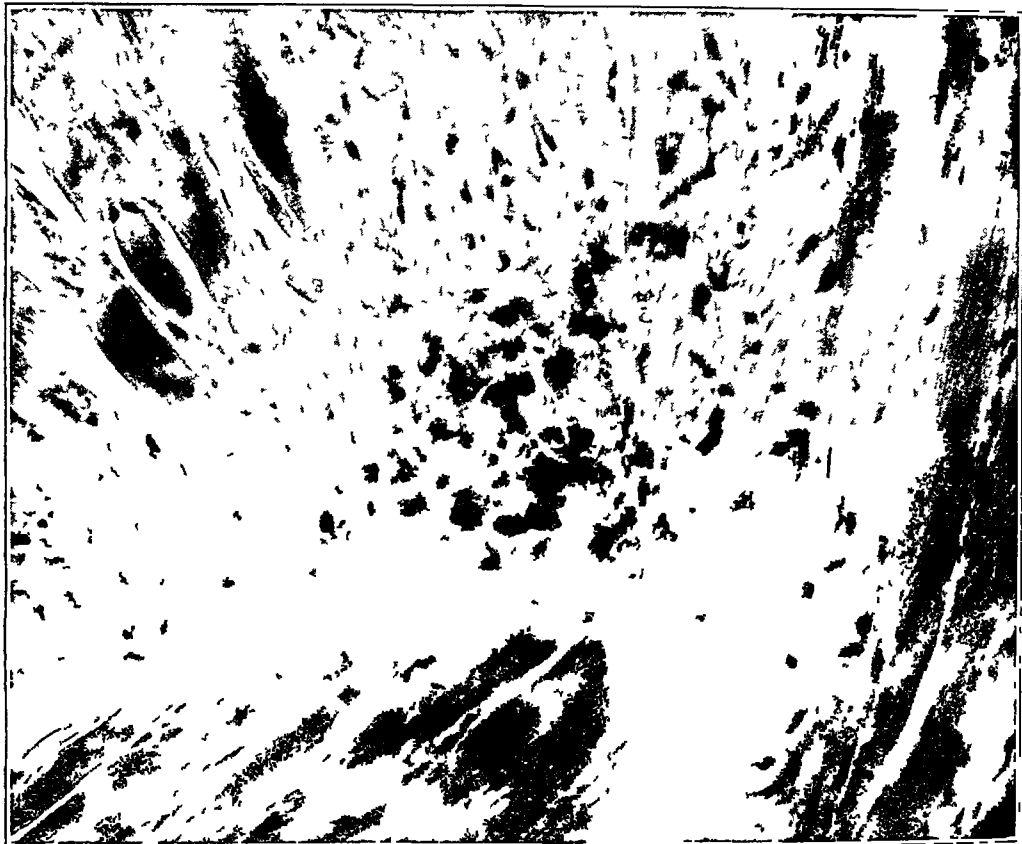


Fig 5 (case 2) —Photomicrograph of a frozen section of a young, fan-shaped Aschoff body which is located in an intermuscular septum and composed of the typical cells with large nuclei. Under higher magnification the condensation of chromatin in the center of the nucleus is seen distinctly. The collagenic ground substance between the cellular elements of the nodule exhibits a fibrinoid swelling. There are edematous loosening and increased cellularity of the connective tissue comprising the septum. Hematoxylin and eosin stain, magnification,  $\times 300$ .

droplet, a few of the myelocytes were necrotic. There were erythrogonia 4 per cent, erythroblasts 20 per cent and normoblasts 49.5 per cent. The normoblasts varied considerably in size, and some of them were large. There were 7 per cent lymphocytes, 3.6 per cent plasma cells, 5.6 per cent monocytoïd cells and 2 per cent histiocytes. Many of the last cells contained erythrocytes. There were 2 per cent megakaryoblasts and 4 per cent megakaryocytes. The megakaryocytes

showed different stages of degeneration, and a few of them were necrotic, in the degenerated cells the cytoplasm was oxyphilic and free from granules. Many megakaryocytes contained erythrocytes or nucleated cell forms. In addition to the loosely scattered lymphocytes there were many well defined lymph follicles.



Fig 6 (case 2)—Photomicrograph of a frozen section of a fully developed, spindle-shaped Aschoff body. Because of beginning regressive changes the characteristic condensation of the chromatin is not as pronounced as in figure 5. There is more fibrinoid material in this nodule than in the one pictured in figure 5. Hematoxylin and eosin stain, magnification,  $\times 600$ .

In the subepicardial fat tissue of the myocardium many free mononuclear cells with ample cytoplasm were seen between the fat cells. There were small, focal accumulations of lymphocytes. An increased number of large free histiocytes



were also noted in the interstitial septums of the myocardium. In addition to these cells there were single nodular accumulations of large protoplasmatic cells with myocytic nuclei. The largest of these cells contained several nuclei. The cells were arranged about a pale, pink-stained fibrinoid center. These nodular accumulations exhibited the characteristic appearance of Aschoff bodies (figs 5 and 6). The muscle fibers were fairly well preserved except for the presence of very small interstitial scars in which the muscle fibers were replaced by elongated cells containing light brown pigment granules. No change was present in sections of the leaflets of the mitral valve.

The glomeruli of the kidneys appeared large and cellular, and the blood content of the tufts was markedly diminished. Most of the cells in the tufts had elongated nuclei. Bowman's space was empty and was often obscured by the swollen tufts. The tubular epithelium showed granular swelling and in places a small amount of fat. There was marked diffuse capillary hyperemia, and the stroma was edematous. The intima of the medium-sized arteries was slightly thickened.

*Bacteriologic Studies*—Cultures made post mortem yielded (a) from the membrane and tonsillar area, a heavy growth of *Str. viridans*, and (b) from the spleen, both a green-producing streptococcus and a hemolyzing streptococcus.

*Anatomic Diagnosis*—The diagnosis was sepsis lenta, chronic tumor of the spleen with recent anemic infarct, cloudy swelling of the liver and the myocardium, Aschoff bodies in the myocardium, hyperplasia of the abdominal, cervical and inguinal lymph nodes, acute glomerulonephritis, pseudomembranous tonsillitis and pharyngitis, passive congestion and edema of the lungs, severe generalized anemia, subicteric discoloration of the skin and scleras, nodose goiter, deforming arthritis of the joints of both hands, hemorrhagic corpus luteum cyst.

#### COMMENT

In most of the cases of Felty's and related syndromes previously reported, the clinical manifestations were particularly emphasized. In a few instances isolated bacteriologic investigations were made post mortem and only occasionally during life. In instances in which necropsy observations were recorded, the data were generally restricted to gross alterations. If microscopic studies were made, the descriptions generally were inadequate. In no instance in the literature, so far as could be ascertained, are more or less complete clinical, bacteriologic and anatomic observations available. In both cases recorded the opportunity was afforded us of studying the patients clinically over a period of time, of making bacteriologic investigations during life and also post mortem and of examining the autopsy material in detail both macroscopically and microscopically.

The first case reported here can be assumed from the clinical standpoint to be one of a chronic sepsis. In fact, the picture for several months was almost identical with that of subacute bacterial endocarditis. From the bacteriologic point of view the recovery of *Str. viridans* from the blood stream during life and from the spleen after death lends support to the clinical assumption. The anatomic changes, especially those

demonstrated by the microscopic examination, speak for a long-standing low grade infection, since they are typical of the alterations observed in sepsis lenta (Siegmund<sup>57</sup> and Jaffé<sup>58</sup>) These changes include activation of the endothelium, noted especially in the spleen, liver and lymph nodes and indicated by the swelling, increase in number and desquamation of the endothelial cells, erythrophagocytosis, distinct increase in the plasma cells in the spleen, lymph nodes and especially in the bone marrow, injury to the bone marrow elements and particularly the granulocytes, subacute glomerulonephritis, evidences of myocarditis, and hemorrhages into the cutis

The considerations in the second case led to conclusions similar to those arrived at in connection with the first case The existence of sepsis, although originally overlooked by the attending physicians, hardly could be questioned Even during the patient's first stay in the hospital febrile periods were recorded The bacteriologic observations likewise point to the presence of sepsis They include the positive results from cultures of the blood for *Sti viridans* before and after the onset of severe symptoms, cultivation during life of green-producing and hemolytic streptococci from the membrane in the throat, a heavy growth of *Str viridans* from the throat and tonsillar area after death, and isolation of green-producing and hemolytic streptococci from the spleen at necropsy (the hemolytic streptococci are considered secondary invaders) The morbid anatomy, especially the microscopic aspect, although differing somewhat from that of the first case, is also characteristic of sepsis lenta Several features, however, warrant special comment

In case 2 the reticulo-endothelial activation had apparently subsided, and in the spleen the fibrillar hyperplasia was seen to predominate over the cellular hyperplasia These changes were older than those observed in case 1 and represent an advanced stage of the same pathologic process Further differences between the two cases are explained on the basis of the extramedullary erythropoiesis, which occurred in the second patient as a result of the extreme injury to the bone marrow The changes in the hematopoietic system with special reference to agranulocytosis have been dealt with elsewhere (Jaffé,<sup>59</sup> case 8) Of special interest were the typical Aschoff bodies observed in the myocardium We do not wish at this time to enter into the vexed question of the histologic specificity of these nodes Suffice it to say that our own

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57 Siegmund, H Ueber einige Reaktionen der Gefasswände und des Endokards bei experimentellen und menschlichen Allgemeininfektionen, Verhandl d deutsch path Gesellsch 20 260, 1925

58 Jaffe, R H The Reticulo-Endothelial System, in Handbook of Hematology, edited by H Downey, New York, Paul B Hoeber, Inc, to be published

59 Jaffé, R H Bone Marrow in Agranulocytosis (Pernicious Leukopenia), Arch Path 16 611 (Nov) 1933

observations lead us to believe with Clawson<sup>60</sup> and others that although characteristically noted in rheumatic fever the Aschoff nodule is not strictly limited to this condition. The specific response of the tissues rather than the type of invading organism is apparently the determining factor.

The evidence obtained in these two cases indicates that Felty's and related syndromes are special forms of sepsis lenta. The variations in the clinical picture and course can be readily explained by differences in the defensive response on the part of the individual tissues and the host as a whole. For instance, in case 1 of this report, it may be assumed that the infection was present for several years, during which time the patient's resistance was relatively high. In the last few months of his illness, however, the defense mechanism gradually became inadequate, and the sepsis progressed slowly until death. In the second case also the infection was of long standing. Here, however, a complete collapse of the protective mechanism occurred suddenly, whereupon the patient became rapidly overwhelmed by the sepsis and died a few days later. Whether a streptococcus and particularly one of the viridans type is the sole cause of Felty's and related syndromes is difficult to state. It can be stated, however, from the evidence at hand that the preponderance of bacteriologic evidence points to a green-producing streptococcus as the usual etiologic organism. In the light of the results reported in connection with studies on arthritis (Archer<sup>61</sup>), skepticism might be expressed in drawing conclusions based on bacteriologic observations alone. However, by inference, support can be adduced from other sources. It is universally accepted that subacute bacterial endocarditis is generally caused by *Str. viridans*. Since the morbid anatomy in our two cases is almost identical (except for the endocardial involvement) with that observed in Schottmüller-Libman's disease, a similar etiology seems quite plausible.

The evidence for assuming the presence of sepsis at the time of necropsy seems indisputable. However, the assumption that the disease begins as a septicemia due to the same organism years previously is open to question. Two observations lend support to the view that the disease from its inception is due to one and the same organism which is responsible for a single pathogenetic process. In the first place, the histologic changes observed at necropsy in our two cases are practically identical with those noted in cases of established sepsis lenta lasting over a period of several months or even years. In the second place the histologic picture of tissue, especially splenic tissue, removed from

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60 Clawson, B. J. The Aschoff Nodule, *Arch. Path.* **8** 664 (Oct.) 1929.

61 Archer, B. H. Chronic Nonspecific Arthritis. Etiology and Treatment, with Special Reference to Vaccine Therapy, *J. A. M. A.* **102** 1449 (May 5) 1934.

patients who undergo surgical operation relatively early in the course of the disease (i. e., with reference to progression) resembles that in case 1 very closely. For example, in sections of the spleen removed at operation by Hanrahan and Miller the following changes were described: activation of the endothelial cells lining the sinuses, erythrophagocytosis, and increase in the number of plasma cells and probably in the number of reticulum cells of the pulp. These were the outstanding features noted in the spleen in case 1, and, indeed, an exchange of slides indicates that the process is probably an identical one (Hanrahan<sup>62</sup>). It will be remembered that splenectomy was performed by Hanrahan and Miller<sup>2</sup> at a time when the patient's general condition was comparatively good and the infectious process was practically stationary. In the case reported by Craven<sup>4</sup> the histologic description as well as the illustrations conform to the picture observed in case 1 and in the case reported by Hanrahan and Miller. Thus it is seen that the changes noted post mortem in our cases were similar to those observed in spleens removed at operation relatively early in the course of the illness. We feel inclined to believe, therefore, that the terminal picture in the cases recorded was not due to a superimposed infection but rather represented the end-stage of a single infection in which the defense mechanism of the host had collapsed.

#### SUMMARY AND CONCLUSIONS

A syndrome observed in adults comprising deforming arthritis, splenomegaly, lymphadenopathy, leukopenia and pigmentation was described in 1924 by Felty. This combination of symptoms has been observed since by other American writers who have applied the name of Felty's syndrome to the condition. In reviewing the world's literature one finds descriptions in European publications of cases in adults with similar clinical pictures referred to as instances of Chauffard's or Still-Chauffard's disease. The condition is generally thought to be the counterpart in adults of Still's disease in children.

A survey of the literature relating to the etiology of Felty's and associated syndromes yields a diversity of views, although a low grade sepsis is the cause favored by most writers. However, only a few disconnected bacteriologic and other observations have been adduced in support of this opinion. In two patients with the typical clinical picture of Felty's syndrome the opportunity presented itself for detailed study ante mortem as well as post mortem. In each instance the bacteriologic and anatomic evidence pointed to the presence of sepsis lenta.

On the basis of the data obtained in connection with the study of these two patients together with a review of the literature, it is believed that the several syndromes which include deforming arthritis and

62 Hanrahan, E. M., Jr. Personal communication to the authors.

lymphadenopathy or splenomegaly represent different forms of the same disease. The underlying sepsis affects not only the joints but also the hematopoietic system, viz, the spleen, liver, bone marrow and lymph nodes. The variable response of the different tissues of the host determines the symptomatology and accounts for the different clinical pictures observed. The usual etiologic organism is believed to be a streptococcus of the viridans type. It is likely that other bacteria can occasionally produce Felty's and allied syndromes.

# HOW ARTERIES COMPENSATE FOR OCCLUSION

## AN ARTERIOGRAPHIC STUDY OF COLLATERAL CIRCULATION

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Nature is lavish in her methods of protecting an organism against harm. One of these methods is the production of tissue in excess of that which is needed for the normal function of an organ. The thyroid, parathyroid and adrenal glands, the kidneys, the pancreas, the testes and the ovaries are excessive, anatomically and functionally. Small amounts of these organs can function as units which are entirely adequate for normal demands.

Morgagni<sup>1</sup> made the first anatomic observations on the development of collateral circulation. These observations were added to by the experimental studies of John Hunter,<sup>2</sup> who ligated the main artery of the rapidly growing antler of a deer. The result was not a cessation of growth but rather a rapid appearance of many enlarged arteries, which carried the blood around the obstruction.<sup>3</sup>

It is not surprising that the arterial circulation is equipped with safeguards. The integrity of a limb depends on the arterial circulation to the extent that the limb cannot survive marked deficiency of the arterial circulation. The relation of some of these safeguards is the purpose of this paper. Patients who were afflicted with thrombo-angitis obliterans were studied.

### THE TECHNIC OF ARTERIOGRAPHY

Roentgenologic visualization of the peripheral arteries of living subjects has become a commonplace procedure. Briefly stated, the method consists of the injection of an opaque substance and exposure of a roentgenographic film under the extremity to the roentgen rays while the opaque medium is in the arteries. The exact technic, value and uses of arteriography and the substances which are used for intra-arterial injection have been reviewed elsewhere.<sup>4</sup>

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From the Division of Medicine, The Mayo Clinic

1 Morgagni, quoted by Mulvihill and Harvey<sup>3a</sup>

2 Hunter, John, quoted by Mulvihill and Harvey<sup>3</sup>

3 Mulvihill, D A, and Harvey, S C. The Mechanism of the Development of Collateral Circulation, *New England J Med* **204** 1032 (May 14) 1931

4 Allen, E V, and Camp, J D. Arteriography. A Roentgenographic Study of the Peripheral Arteries of the Living Subject Following Their Injection with a Radiopaque Substance, *J A M A* **104** 618 (Feb 23) 1935

## THE NORMAL ARTERIOGRAM

The roentgenographic appearance of normal arteries is characteristic.<sup>4</sup> From the forearm the radial and ulnar arteries proceed to the hand, where they form the palmar arches. The interosseous arteries usually end in branches proximal to the wrist, but occasionally they pass into the hand. The digital arteries arise from the palmar arches and bifurcate at the approximate level of the metocarpophalangeal joints to course along the lateral surfaces of the digits. In the forearm and hand rather numerous fine short branches may be seen. In the fingers fewer branches are seen. Not infrequently small branches of the ulnar or radial arteries may be seen, which arise proximal to the level of the wrist and run distally to the hand.

## THE COLLATERAL CIRCULATION

The term collateral is used in this study to indicate arteries and evidence of circulation in arteries which ordinarily are not seen in roentgenograms of the extremities of persons who do not have arterial disease. One who studies arteriograms of patients with occlusive arterial disease cannot avoid being impressed with the marvelous capacity of the circulation to compensate for the occlusion of arteries. It is obviously this compensatory or collateral circulation which prevents gangrene in many cases of occlusive arterial disease. It also follows that restoration of a rather normal arterial circulation in cases in which there is chronic arterial occlusion depends on the establishment of collateral circulation.

The chief characteristics of collateral arteries are the irregular, turning and twisting course which they pursue, their variation in size in any selected area, their apparent purposeless crossing and recrossing, their lateral course in areas in which they are profuse, and their anastomosis (fig 1). These arteries are in contrast to normal arteries, which pursue a direct and largely longitudinal course, with a minimum of crossing, which are more constant in size in any specific area and which manifest a minimum of anastomosis with each other.

## METHODS OF ESTABLISHING COLLATERAL CIRCULATION

*Anastomosis*—When an artery is partially occluded a large collateral branch may arise from it above the point of occlusion. The collateral artery passes at right angles to the parent artery for a short but variable distance and then turns abruptly to run roughly parallel to the course of the diseased artery. Distal to the point of occlusion it turns sharply and joins the parent artery at right angles (fig 2A). When occlusion of the diseased artery is complete the collateral artery carries the blood around the occlusion in a fairly adequate manner, as shown

by normal filling of the artery distal to the point of its occlusion (fig 2 *B*) I have never observed anastomosis of two main parallel arteries in the arteriogram of a normal person. It occurs infrequently but occasionally, in cases of thrombo-angitis obliterans. Direct communications have been observed between the interosseous and the radial arteries and between the interosseous and the ulnar arteries (fig 2 *C*)

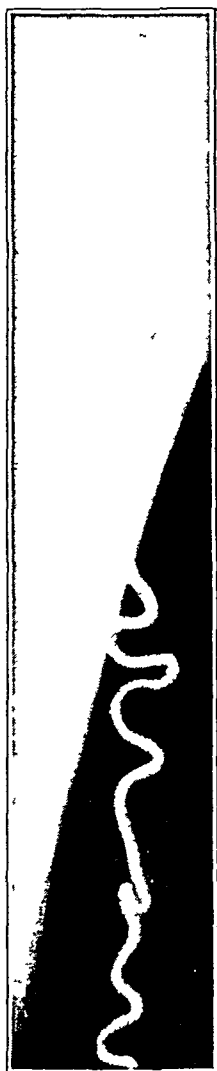


Fig 1—A collateral artery characterized by a turning and twisting course

*Lateral Branching*—Occlusion of a digital artery with minimal involvement of its companion artery is frequently seen. In such instances the artery which is not diseased sends numerous branches laterally to the site of the diseased artery. These collateral arteries are numerous and seem to supply the tissues which have been deprived of their normal blood supply in an adequate manner. Some of them may join unoccluded portions of the diseased artery to form cross-anastomoses (fig 3). Lateral branching from the unoccluded portion of an



artery may compensate for occlusion of a companion artery. I have observed that a branch of the radial artery may cross to the ulnar side of the wrist when the ulnar artery is occluded (fig 2 C)

*Prolongation*—Ordinarily, the interosseous arteries do not extend beyond the wrist. When the radial and ulnar arteries are occluded

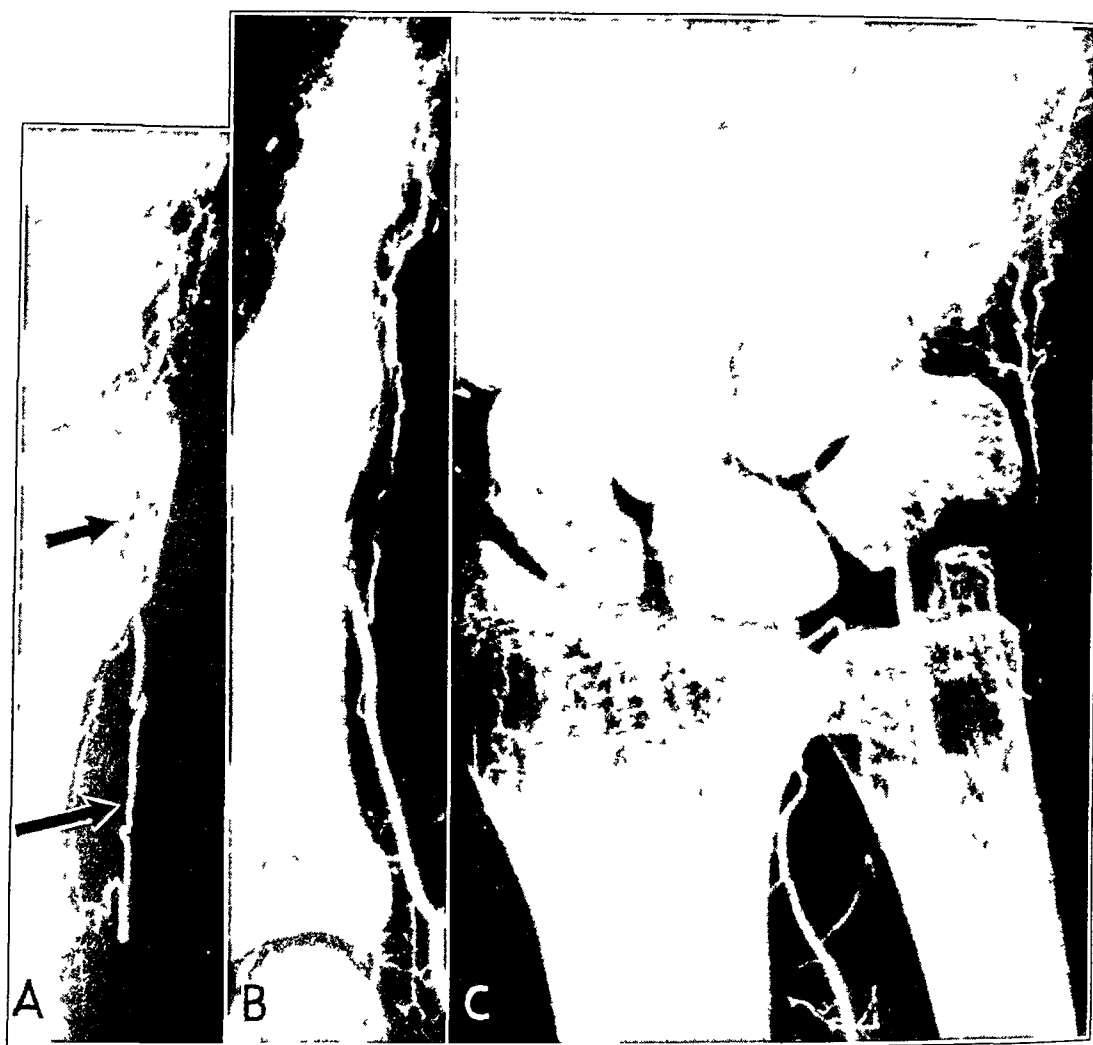


Fig 2—Collateral circulation by anastomosis. In A the distal arrow indicates partial occlusion of a radial artery. The proximal arrow indicates a collateral artery which joins the radial artery distal and proximal to the area of partial occlusion. In B a small collateral artery connects portions of the digital artery distal and proximal to the area of occlusion. In C, showing collateral circulation by lateral branching, the ulnar artery has been occluded proximally. A collateral branch passes from the radial artery to the ulnar side of the wrist. The interosseous artery is connected with the radial and ulnar arteries by direct anastomosis.

above this level, the branches of the interosseous arteries invariably extend down to the hand. The branches arise from the distal end of the interosseous arteries and extend out to both the radial and the ulnar

side of the wrist as well as distally to join with collateral arteries in the hand (fig 4) This is a fortunate provision because, in my experience, the interosseous arteries are almost never occluded It possibly explains why gangrene of the foot is not uncommon in cases of thrombo-angitis obliterans, while gangrene of the hand never occurs

*Terminal Branching*—When an artery is occluded throughout a considerable portion of its course, numerous branches may arise from above



Fig 3—Collateral circulation by lateral branching The digital artery on the left has been occluded segmentally Many collateral branches pass laterally from the digital artery on the right

the area of occlusion and pass distally in a direction roughly parallel to that of the diseased artery In a case of occlusion of the middle and distal thirds of the femoral artery and of the popliteal artery, large collateral branches which arose from the unoccluded portion of the femoral artery, were observed to pass to a level well below the knee

*The Network of Collateral Arteries*—In some cases in which occlusion of the normal arteries has been extensive, particularly in the palm, the arteries are represented by an irregular network of crossing branches, the origin, direction and termination of which are difficult or impossible to determine (fig 5) It is probable that in this confusing network of collateral arteries all the methods for establishing collateral arteries, which have been described previously, are utilized



Fig 4—Collateral circulation by prolongation The radial and ulnar arteries are occluded The interosseous artery extends distally into the hand and sends branches to the radial and ulnar sides of wrist

#### COMMENT

It is obvious from this study that collateral circulation is profuse in cases of occlusive arterial disease Logical and purposeful design in the development of collateral circulation is apparent, for without the

ability to develop collateral circulation the integrity of limbs would be seriously endangered by comparatively minor degrees of arterial occlusion. It is of interest that the methods by which embarrassment of the circulation results from arterial occlusion is overcome in the extremity are about the same as those which an engineer would use to surmount similar obstacles in hydrodynamics. If a segment of a stream was occluded by a dam which could not be removed, what would be more



Fig 5—Collateral circulation by network formation. The normal arteries in the hand have been occluded. Circulation is maintained by a network of arteries.

logical than the construction of a canal around the dam, thus reestablishing the continuity of the stream (fig 2 *A* and *B*)? Or if one of two parallel canals was irremediably destroyed, how could the problem be better solved than by sending branches out laterally from the unoccluded canal to the area which ordinarily was supplied by the one which was destroyed (fig 3)? For every method of overcoming arterial occlusion, as seen in the arteriogram, there exists a logical parallel procedure to overcome a similar obstacle in hydrodynamics.

Neither this observation nor Hunter's statement that "the blood goes where it is needed" satisfactorily answers questions about the origin of collateral circulation<sup>3</sup> How do collateral arteries develop? Are they constructed anatomically in situ, or do they represent increased function in arteries which already exist? A somewhat analogous situation exists in the glomeruli of the kidney, only a small percentage of these function at any one time

Contrast of the arteriograms of normal limbs of the living subject with the arteriograms of limbs which have been amputated for reasons other than arterial disease<sup>5</sup> reveals marked differences In the latter condition the number of arterial branches and the surface area which is occupied by the arteries are much greater than those which are seen in arteriograms of normal living subjects This is evidence that a great many arterial branches which are not visible in the arteriogram of living subjects exist nevertheless This failure to render many existing arteries visible in the arteriograms of living subjects is apparently not a defect of the method, these arteries apparently are not functioning Further evidence for this assumption is offered by the experimental work of Horton and Craig,<sup>6</sup> who made arteriograms of the hindlegs of dogs, on some of which sympathectomy had been performed The surface area which was occupied by arteries was much greater in the limbs in which sympathetic denervation had been performed than it was in the normal control limbs It is a common observation that blocking of the sympathetic impulses to an extremity by anesthesia or by operation leads to an immediate and sharp increase in the temperature of the part, a manifestation of increased circulation This is almost certain evidence of increased function of the arteries, which existed in a partial or complete resting state before the interruption of the sympathetic impulses was effected

Mulvihill and Harvey<sup>3</sup> have demonstrated that after ligation of the external iliac artery the temperature of the leg of a dog drops rapidly to the level of the temperature of the room After a few hours the temperature rises rather abruptly to that of the control limb Further experiments demonstrated that if sympathectomy was performed before ligation of the artery no decrease in the temperature occurred when ligation was performed, and if sympathectomy was performed when the temperature was low, as a result of ligation of the artery, the extremity immediately became as warm as the normal member These experi-

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5 Horton, B T A Study of the Vessels of the Extremities by the Injection of Mercury, *S Clin North America* **10** 159 (Feb ) 1930

6 Horton, B T, and Craig, W McK Evidence Shown in the Roentgenograms of Changes in the Vascular Tree Following Experimental Sympathetic Ganglionectomy, *Arch Surg* **21** 698 (Oct ) 1930

ments offer convincing evidence of the major rôle of the vasomotor component in establishing collateral circulation, and when considered with other data which have been presented briefly in the preceding paragraphs, they indicate that, in the main, collateral arteries which are seen in the arteriograms of living subjects who have thrombo-angitis obliterans are arteries which were present before the onset of the arterial disease. The function and hence the size of these arteries was increased, apparently to compensate for occlusion in the main arteries.

#### SUMMARY

Collateral circulation may be very profuse in cases of thrombo-angitis obliterans. By methods which have been designated as anastomosis, lateral projection, prolongation, terminal branching and network formation, a collateral circulation develops which can compensate for extensive occlusion of the chief arteries of an extremity. There is indirect but entirely logical and convincing evidence that collateral arteries are chiefly arteries which are present normally but which have increased in size as a response to a demand for increased function which arises as a result of occlusion of the main arteries.

# PNEUMOTHORAX THERAPY IN EXPERIMENTAL LOBAR PNEUMONIA IN THE DOG

WITH A REPORT OF A CASE IN MAN

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AND

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The treatment of lobar pneumonia, both experimental and clinical, with artificial pneumothorax has lately been revived with enthusiasm. The present studies were undertaken to see whether we could corroborate the success reported with the use of pneumothorax in the treatment of experimental lobar pneumonia in the dog.

## EXPERIMENTAL PROCEDURE

Healthy dogs weighing from 8 to 12 Kg were used.

*Pneumococcus*—The method first devised by Coryllos and Birnbaum<sup>1</sup> was used. From 20 to 30 cc of an eighteen to twenty-two hour broth culture of *Pneumococcus* type I, II or III was centrifugated, and the sediment was suspended in 1 cc of the supernatant broth. The suspension was then sprayed by gentle air pressure through a 2 mm brass tube over the mouth of the bronchus of the lower lobe. The bronchoscope was used to locate the bronchus. In some cases the sediment was suspended in liquefied 15 per cent agar broth instead of in plain nutrient broth and injected into the bronchus. After insufflation of the culture the bronchoscope was removed, and the animal was placed on its right side in a warm room till the return of consciousness.

*Anesthesia*—An injection of 55 milligrams of amytal (iso-amylethyl barbituric acid) per kilogram of body weight in the form of a 10 per cent solution of sodium amytal was given intraperitoneally.

*Pneumothorax*—From 200 to 350 cc of air was injected under manometric control, usually in the fifth interspace in the postaxillary line.

*Blood Cultures*—Approximately twenty-four hours after the culture of *Pneumococcus* was insufflated into the lung, 2 cc of blood was drawn from the vein of the leg under sterile precautions for culture on plates of poured agar broth. With a few exceptions, the blood from the heart was cultured at autopsy. In our tables the reports on the cultures of the blood taken after twenty-four hours and those on cultures of the blood from the heart taken at autopsy are differentiated. When either culture was positive it was stated in the tables of analysis that the animal had bacteremia.

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From the Department of Surgical Research, Cornell University Medical College. This work was aided by a gift from Mrs. John L. Given in support of surgical research.

1 Coryllos, P. N., and Birnbaum, G. L. Lobar Pneumonia Considered as a Pneumococcic Lobar Atelectasis of the Lung. *Bronchoscopic Investigation*, Arch Surg 18:190 (Jan) 1929.

## ANALYSIS OF EXPERIMENTAL DATA

Forty animals were used in the experiment. Table 1 presents a general summary. It will be noted that there were three moribund dogs in the whole series, two in the group of untreated (control) animals and one in the group of dogs receiving pneumothorax. By "moribund" we mean comatose, nearly always subnormal temperature accompanied the coma. All three moribund dogs had bacteremia and succumbed. In four animals which died, the lungs were normal at autopsy, two (dogs 35 and 41) had received pneumothorax, and two (dogs 60 and 62) had not.

Of the first two animals, which were ailing until they died, in fifty-six and fifty-seven days, respectively, one had bacteremia at the start of the illness and at death, the other had no bacteremia at the beginning or at death. Both the other two animals (dogs 60 and 62) in the group of controls appeared clinically well on the fourth day, but they were found dead, one on the thirty-fifth and one on the thirty-eighth day, both had had bacteremia. All four deaths were classed as due to experimental factors. Still another animal in the group of controls (dog 56) appeared clinically well on the fourth day but was found dead on the twenty-sixth day, this animal had bacteremia at the start. The autopsy revealed pathologic changes due to pneumococcus in the lower and middle lobes of the right lung. One animal (dog 55) in the group receiving pneumothorax appeared well at the end of six days but was found dead on the one hundred and twelfth day, although the dog had had bacteremia at the start the outcome was recorded as recovery from experimental pneumonia with the use of pneumothorax, the cause of death not being revealed at autopsy.

For the sake of brevity in the analysis, the term "toxic" is used to indicate toxicity of a moderate or high degree or moribundity (tables 3 to 8). It will be noted that fifteen of the seventeen animals given pneumothorax were very sick (group of toxic animals), one of these being moribund. Of the remaining twenty-three dogs, which did not receive pneumothorax, only eleven were very sick, two of which were moribund. For this reason, analyses were made of data on animals with a comparable degree of toxicity, as the tables show.

Tables 2 to 10 reveal the following facts:

1. For the total number of forty animals, the incidence of bacteremia was 37 per cent and the mortality 37 per cent.

2. For the fourteen animals showing little or no toxicity, the incidence of bacteremia was 14 per cent and the mortality 7 per cent. The twelve animals in this group which did not receive pneumothorax recovered.



TABLE 1—General Summary of Experimental Data on Forty Lobar Pneumonia Was Induced with the Results of Pneumothorax Therapy

Dog	Weight, Kg	Volume of Sedimented Pneumococci Suspended in Broth, Cc	Type of Pneumococcus	Lobe of Right Lung in Which Pneumonia Was Induced in 24 Hrs	Degree of Clinical Toxicity	Clinical Course	Results of Blood Culture	Observations 24 Hours After Insufflation			Postmortem Observations	Comment
								Temperature, °F	Pulse Rate	Respiratory Rate		
1,001	10	0.05	I	Lower	Slight	Very well 2 days after culture was given, recovery	Negative	39.2 (102.6 F)	90	40		
1,002	10.5	0.05	I	Lower	None	Very well, recovery	Negative	39.4 (102.9 F)	100	35		After pneumothorax pulse rate rose to 120, respirations to 60 (shallow), 2 days after first pneumothorax temperature 39.6 C (103.3 F), pulse 90, respirations 40
1,003	10.5	0.5	I	Lower, middle	Moderate to high	Slight improvement 2 days after culture was given, recovery	Negative	39.2 (102.6 F)	100	30	250	After pneumothorax respiratory rate rose from 30 to 50, death in 24 hours after pneumothorax, coma
1,004	10	0.05	I	Lower	Moribund	Coma, death 24 hrs after pneumothorax	1 colony on plate, heart blood 200 colonies	36.1 (96.98 F)	80	30	300	After pneumothorax respiratory rate rose from 30 to 50, death in 24 hours after pneumothorax, coma
1,006	10	0.05	II	Lower	Very high	Very well 2 days after culture was given, recovery	Negative	39.6 (103.3 F)	150	50	250 250	After pneumothorax respiratory rate rose from 30 to 60, 2 days after first pneumothorax, temperature 39.4 C (102.9 F), pulse 95, respirations 40
1,005	10	0.05	II	Lower	Slight	Very well 2 days after culture was given, recovery	3 colonies on plate	38.4 (101.1 F)	100	26		
1,007	10	0.05	II	Lower	None	Very well, recovery	Negative	38.6 (101.5 F)	150	60	250 350	After first pneumothorax respirations rose from 60 to 70, 3 days after first pneumothorax, temperature 39.2 C (102.6 F), pulse 100, respirations 60 (grunting respiration)
1,008	10	0.05	I	All	Very high	Moderately ill respiration labored 3 days after culture was given, recovery	Negative					
1,011	6	0.035	I	Lower	Slight	Very well 2 days after culture was given, recovery	Negative	39.0 (102.2 F)	110	56		

1,012	10	0 06	I	Lower	Slight	Very well 2 days after culture was given, recovery	Negative	100° (106° F.)	95	65	
1,013	12	0 07	I	All	Moribund	Coma, death 21 hrs after culture was given	Heart blood 1 colony on plate	96.0° (96.8° F.)	90	60	
1,014	14	0 07	I	Lower	Very high	Much improved 2 days after culture was given	Negative	99.6° (103° F.)	100	10	
1,020	10	0 06	I	Lower, middle	Very high	Very well 4 days after culture was given	Negative			300	Shown considerable resistance before pneumonia, staggering around room
1,023	10	0 05	I	Lower	Very high	Very well 2 days after culture was given, recovery	Negative				
1,024	10	0 05	I	Lower	None	Very well, recovery	Negative				
1,026	10	0 05	I	Lower	Very high	Much improved 2 days after culture was given, recovery	Negative			200 300	
1,025	10			Lower	Slight	Very well, recovery	Negative				
1,033	10	0 05	I	Lower	Slight	Very well 2 days after culture was given, recovery	Negative				
1,034	10	0 05	I	Lower, middle?	Moderately high	Improved 2 days after culture was given, recovery	Negative			400 275	
1,035	8	0 07	I	Lower	Very high	Improved 2 days and worse 3 days after culture was given, ailing until death on fifty seventh day	2 colonies in 18 hrs., 60 colonies heart blood	99.2° (102.7° F.)	120	10	Lungs normal
1,036	8	0 07	I	Lower	None	Very well, recovery	Negative				
1,037	8	0 07	I	Lower	Very high	Very well 2 days after culture was given, recovery	Negative	99.4° (102.9° F.)	100	50	
1,038	10	0 07	I	Lower	None	Very well, recovery	Negative				
1,039	10	0 05	III	Lower, middle?	Very high	Much improved 3 days after culture was given, recovery	1 colony in 18 hrs	99.4° (102.9° F.)	100	60	
1,040	10	0 05	III	Lower, middle	Slight	Quite ill on third day, improved 5 days after culture was given, recovery	Negative	99.8° (103.6° F.)	100	10	
1,041	10		III	Lower, middle	Very high	Improved on second day, worse third day after culture was given, ailing until death on fifty sixth day	Negative, heart blood negative (taken at death)	99.4° (102.9° F.)	100	60	Respiration labored after each pneumothorax, 6 days after pneumothorax expiratory grunt, temperature 110° (105.8° F.), pulse 90, respirations 34

TABLE 1—General Summary of Experimental Data on Forty Dogs in Which Lobal Pneumonia Was Induced with the Results of Pneumothorax Therapy—Continued

Dog	Weight, kg	Volume of Sedimented Pneumococci Suspended in Broth, Cc	Type of Pneumococcus	Lobe of Right Lung in Which Pneumonia Was Induced in 24 Hrs	Degree of Clinical Toxicity	Clinical Course	Results of Blood Culture	Observations 24 Hours After Insufflation			Postmortem Observations	Comment
								Temperature,	Pulse Rate	Respiratory Rate		
1,012	8	0.05	III	Lower	Slight	Improved in 2 days and worse 3 days after culture was given, clinically well on seventh day, recovery	Negative	39.6 (103.3 F.)	110	50	200 275	Pneumothorax given on second and third days after culture, respiration increased after each treatment, expiring grunt persisted after second pneumothorax, 5 days after first pneumothorax, temperature 39.0 C (102.2 F.), pulse 95, respirations 50
1,015	8	0.05	III	Lower, middle?	Moderately high	Improved 2 days after culture was given, recovery	Negative	40.1 (101.7 F.)	100	40	300 300	Dyspnea after each pneumothorax, day after first pneumothorax ten respirations 50, pulse 65, after pneumothorax was started temperature 40.1 C, pulse 95, respirations, 15
1,016	8	0.05	III	Lower	Moderately high	No improvement death 7 days after use of pneumothorax was started	Negative	39.6 (103.3 F.)	120	40		After first pneumothorax respiratory rate rose from 10 to 50 day after first pneumothorax, temperature 40 C (106 F.), pulse 120, respirations 60, day more ill 1 day after first pneumothorax, temperature 39.8 C (103.5 F.), pulse 100, respirations 40
1,017	8	0.05	III	Lower	Slight	Worse 2 days and slightly better 3 days after culture was given, death 8 days after pneumothorax was started	Negative, heart blood 200 colonies	41.0 (105.8 F.)	100	40	100 200	Accessory lobe of lower lobe of right lung in stage of red hepatization
1,018	10	0.06	III	Lower, middle	Moribund	Coma, improved in 2 days and better in 3 days after culture was given	1 colony in 48 hrs	39.8 (103.6 F.)	120	1		Red hepatization in lower middle accessory and half of the upper lobes of the right lung
1,051	8	0.06 in 1.5% salt broth	III		Very high	Extreme toxicity continued, death 18 hours after culture was given	1 colonies in 48 hrs	36.1 (96.9 F.)	100	60	250	All lobes of right lung consolidated, reddish gray

1,052	8	0.06 in 1.5% agar broth	III	Upper	Very high	Improved in 2 days, died 7 days after cul- ture was given	Negative	39 S. (103.6 F)	100	40	Lower half of upper and accessory lobes of right lung consoli- dated, fluid over pylori- form sinuses, vomitus in mouth, asphyxia?	Blood from rectum 5 days before death
1,055	9	0.015 in 1.5% agar broth	III	Lower, middle?	Very high	Very ill on second and third days after cul- ture was given, appeared well after 6 days, died in 112 days, reported as clinical recovery	3 colonies in 4 days	39.6 (103.3 F)	90	60	Lungs, heart and ab- domen generally involved	Marked dyspnea after each pneumothorax, on day after second pneumo- thorax dog very sick with dyspnea, temperature 105.5 C (104.9 F), pulse 60, respi- rations 60, 6 days after first pneumothorax ap- peared well, but tempera- ture was 39.7 C (103.5 F), pulse 90, respirations, 50, classified as clinical recovery
1,057	10	0.05 in 1.5% agar broth	III	Lower	Very high	No improvement on second and third days after culture was given or until death 10 days after production pneu- mothorax started	Negative 1 days, heart blood 60 colonies	40.0 (106 F)	100	55	Lower lobe of right lung gray pink, organization	Marked dyspnea after each pneumothorax, on day after second pneumo- thorax, temperature 39.8 C (103.6 F), pulse 95, res- pirations 50, and 6 days after first, temperature 39.4 C (102.9 F), pulse 80, respirations 40
1,056	11	0.05 in 1.5% agar broth	III	Lower	Very high	Appearance good 7 days after culture was given though tempera- ture, pulse rate and re- spiratory rate were 39.4 C (102.9 F), 90 and 40, respectively, found dead on twenty sixth day	25 colonies in 1 days	40.2 (104.6 F)	95	60	Lower half of lower lobe of right lung puru- lent, gray and partly organized, lobe of right middle lung consolidated and pinkish gray	Death classified as due to experimental factors
1,059	9	0.06 in 1.5% agar broth	III	Lower, middle?	Very high	Died 30 hours after cul- ture was given and 7 hours after pneumo- thorax	3 colonies in 48 hrs, heart blood 12 colo- nies in 72 hrs	36.8 (98.2 F)	90	70	All lobes of right lung with red hepatization	Marked dyspnea after pneumothorax
1,060	11	0.065 in 1.5% agar broth	III	Lower	Very high	Very well after 2 days, clinical recovery in 4 days, died in 35 days	3 colonies in 48 hrs	39.4 (102.4 F)	100	60	Lungs normal, cause of death unknown	Death classified as due to experimental factors
1,061	11	0.065 in 1.5% agar broth	III	Lower, middle	Very high	Very well after second pneumothorax, im- proved 3 days after second pneumothorax and died on this day in convulsion	1 colony in 48 hrs, heart blood 60 colonies	40.4 (104.7 F)	100	60	Lower and accessory lobes of right lung with gray hepatization, upper and middle lobes atelectatic, ruptured abscess in lower lobe of right lung not related to pneumothorax	Marked dyspnea, rapid respiration for 1 day after each pneumothorax, spontaneous pneumo- thorax and asphyxia?
1,062	11	0.065 in 1.5% agar broth	III	Lower	Moderately high	Much improved after 2 days, very well on fourth day, died in 38 days	1 colony in 48 hrs	40.4 (104.7 F)	90	50	Lungs normal, cause of death unknown	Death classified as due to experimental factors

TABLE 2—*Relation of the Incidence of Bacteremia to the Incidence of Death*  
(Total Group)

	Number	Dogs Which Died		Dogs Which Recovered	
		Number	Percentage	Number	Percentage
Total number of dogs	40				
Dogs with negative blood cultures	25	3	12	22	88
Dogs with positive blood cultures	15	12	80	3	20
Incidence of bacteremia, 37 per cent					
Incidence of death, 37 per cent					

TABLE 3—*Relation of the Incidence of Bacteremia to the Incidence of Death*  
(Group of Toxic Animals)

	Number	Dogs Which Died		Dogs Which Recovered	
		Number	Percentage	Number	Percentage
Dogs showing toxicity	26				
Dogs with negative blood cultures	12	2	17	10	83
Dogs with positive blood cultures	14	12	86	2	14
Incidence of bacteremia, 54 per cent					
Incidence of death, 54 per cent					

TABLE 4—*Relation of the Incidence of Bacteremia to the Incidence of Death*  
*for Groups of Dogs Not Treated with Pneumothorax and for*  
*Groups of Treated Dogs*

	Number	Dogs Which Recovered		Dogs Which Died	
		Number	Percentage	Number	Percentage
Dogs treated with pneumothorax	15				
Dogs with positive blood cultures	8	1	13	7	87
Dogs with negative blood cultures	7	5	71	2	29
Dogs not treated with pneumothorax	11				
Dogs with positive blood cultures	6	1	17	5	83
Dogs with negative blood cultures	5	4	80	1	20

TABLE 5—*Relation of the Incidence of Bacteremia to the Incidence of Death for*  
*Groups of Dogs Not Treated with Pneumothorax and for Groups*  
*of Treated Dogs (Analysis 2)*

	Number	Dogs With Bacteremia	
		Number	Percentage
Animals showing toxicity	26		
Dogs treated with pneumothorax <sup>3</sup>	15		
Dogs which died	9	7	78
Dogs which recovered	6	7	17
Dogs not treated with pneumothorax	11		
Dogs which died	6	5	83
Dogs which recovered	5	1	20

TABLE 6—*Relation of the Incidence of Recovery for Dogs Not Treated with Pneumothorax to the Incidence for Treated Dogs, Irrespective of Bacteremia*

	Number	Dogs Which Died		Dogs Which Recovered	
		Number	Percentage	Number	Percentage
Animals showing toxicity	26				
Dogs treated with pneumothorax	15	9	60	6	40
Dogs not treated with pneumothorax	11	6	55	5	45

TABLE 7—*Relation of the Incidence of a High Degree of Toxicity for Animals Not Treated with Pneumothorax and That for Treated Animals*

	Number	Dogs Which Were Moribund and Highly Toxic	Dogs Which Were Moderately Toxic	Ratio of the Degrees of Toxicity
Animals showing toxicity	26			
Animals treated with pneumothorax	15	12	3	4 1
Animals not treated with pneumothorax	11	9	2	4 5 1

TABLE 8—*Comparison of Changes in the Indications of Toxicity on the Third Day After Insufflation of Pneumococcus for Dogs Not Treated with Pneumothorax and Those for Treated Dogs*

	Number	Dogs Appearing Worse or Unimproved	
		Number	Percentage
Dogs showing toxicity	26		
Dogs treated with pneumothorax	15	9	60
Dogs not treated with pneumothorax	11	3	37

TABLE 9—*Relation of the Incidence of Bacteremia and the Incidence of Death for a Group of Nontoxic Animals, Irrespective of Treatment with Pneumothorax*

	Total Number	Number of Dogs Which Died	Number of Dogs Which Recovered
Dogs slightly or not toxic	14		
Dogs with bacteremia	2	1	1
Dogs without bacteremia	12	0	12
Incidence of bacteremia, 14 per cent			
Incidence of death - per cent			

TABLE 10—*Relation of Treatment with Pneumothorax to the Incidence of Bacteremia and the Incidence of Recovery for a Group of Nontoxic Animals*

	Total Number	Number of Dogs Which Died	Number of Dogs Which Recovered
Dogs slightly or not toxic	14		
Dogs treated with pneumothorax	2		
Dogs with bacteremia	1	1	0
Dogs without bacteremia	1	0	1
Dogs not treated with pneumothorax	12		
Dogs with bacteremia	1	0	1
Dogs without bacteremia	11	0	11

3 For the twenty-six toxic animals the following data were obtained

(a) The incidence of bacteremia was 54 per cent and the mortality 54 per cent

(b) Sixty per cent of the dogs receiving pneumothorax and 55 per cent of the dogs not receiving pneumothorax died

(c) Eighty-six per cent of the dogs with bacteremia and only 17 per cent of the dogs without bacteremia died

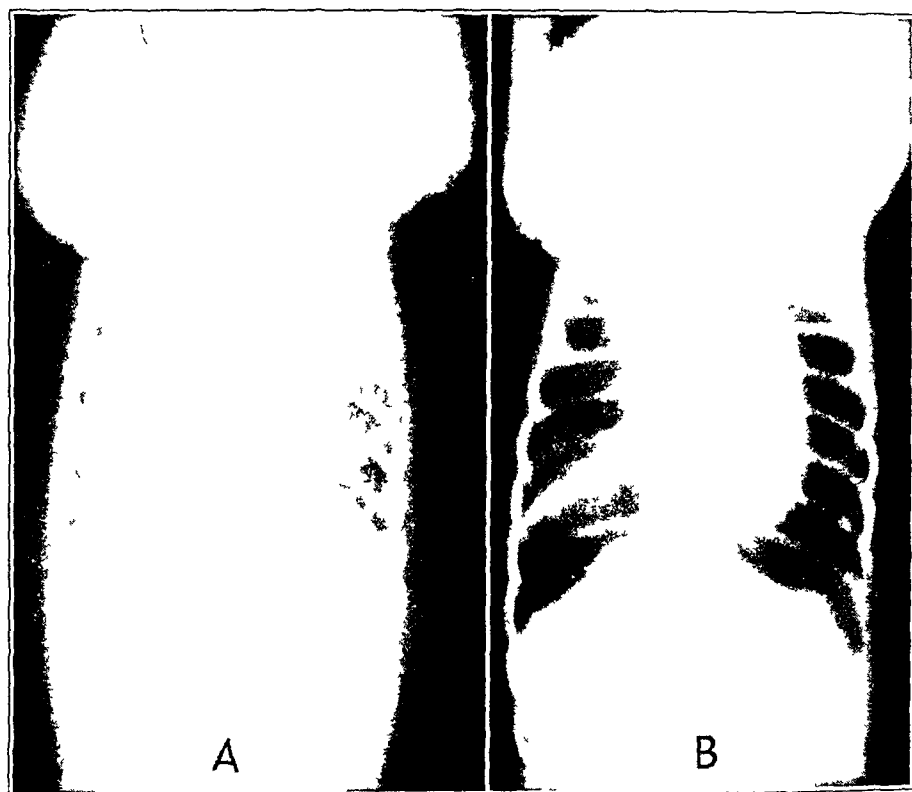


Fig 1 (dog 35) —Roentgenograms of the lungs, showing (A) pneumonia of twenty-four hours' duration in the lower lobe of the right lung and (B) the appearance after the production of pneumothorax on the right side with 350 cc. of air. Bilateral pneumothorax is evident

(d) Of the dogs receiving pneumothorax, 87 per cent with bacteremia and only 29 per cent without bacteremia died

(e) Of the dogs not receiving pneumothorax 83 per cent with bacteremia and only 20 per cent without bacteremia died

(f) Of the dogs receiving pneumothorax 78 per cent of those that died and only 16 per cent of those that recovered had bacteremia

(g) Of the dogs not receiving pneumothorax 83 per cent of those that died and only 20 per cent of those that recovered had bacteremia

## CLINICAL EFFECTS OF PNEUMOTHORAX

The production of bilateral pneumothorax as shown by roentgenograms, was the rule, the flimsy mediastinum of the dog allowing diffusion of gases to the healthy side. The air is especially evident above the diaphragm on the healthy side (figs 1*A* and *B* and 2*A* and *B*). In contrast to the results for the animals with a permeable mediastinum are those for dogs for which roentgenograms of the chest are shown in figures 3 and 4. These plates demonstrate that by the production of a thickened mediastinal pleura the mediastinum of the dog may be made impermeable to gases and (as in these two cases) to fluids. This result was brought about by enclosing the lower lobe of the right lung in a



Fig 2 (dog 61) —Roentgenograms of the lungs, showing (*A*) pneumonia of twenty-four hours' duration in the lower lobe of the right lung, with marked dextrocardia and elevation of the right side of the diaphragm, and (*B*) the appearance after the production of pneumothorax on the right side with 275 cc of air. Dextrocardia is now absent.

rubber balloon, a procedure which results in subacute pleurisy with effusion limited to the right side.

In table 1 the usual failure to obtain relief after treatment with pneumothorax is indicated. In fact, the animals suffered general distress and dyspnea, certainly, we observed no clinical "crisis" after the production of pneumothorax, such as that reported<sup>2</sup> to occur experi-

2 Lieberman, L. M., and Leopold, S. S. Therapeutic Pneumothorax in Experimental Lobar Pneumonia in Dogs, *Am J M Sc* **187** 315, 1934.



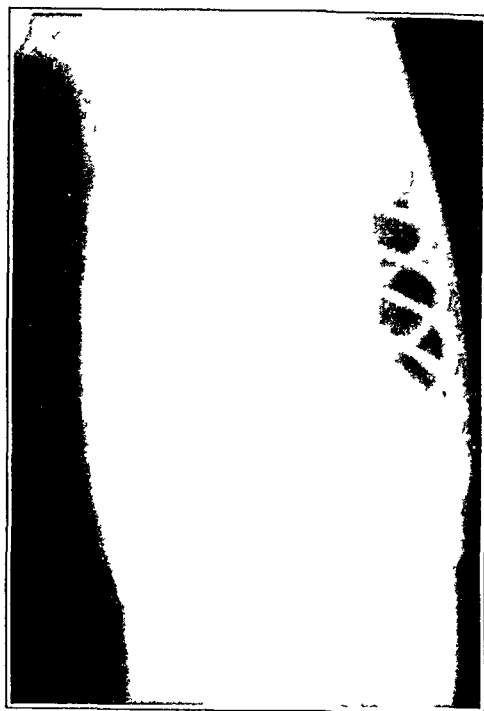


Fig 3 (dog 22) —Roentgenogram demonstrating that the mediastinum of the dog may be made impermeable to gases and fluids by the production of subacute pleurisy with effusion. The effusion is limited to the right side by a thickened mediastinal pleura.

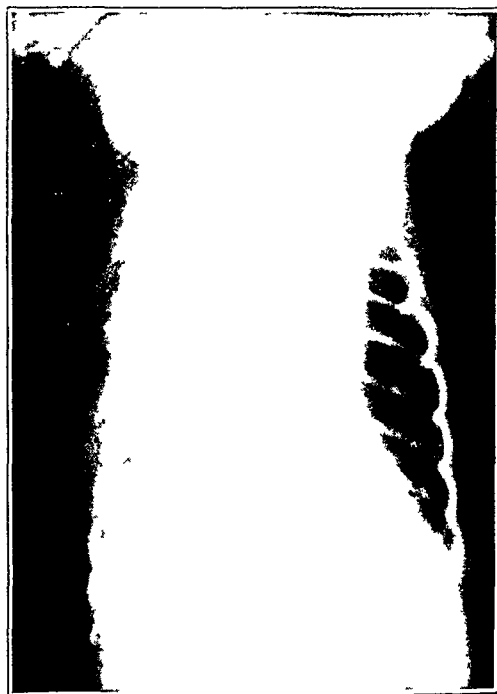


Fig 4 (dog 31) —Roentgenogram illustrating the same result as that shown in figure 3.

mentally within from two to three days after the institution of pneumothorax. From the standpoint of the appearance, the presence of fever and the respiratory rate, nine, or 60 per cent, of fifteen toxic animals receiving pneumothorax were worse or unimproved by the third day after the insufflation of the culture, that is, after the second treatment with pneumothorax. Of equally toxic animals not receiving pneumothorax, eight, or 73 per cent, were definitely improved by the third day. Two animals (dogs 42 and 47) showing slight toxicity were worse after treatment with pneumothorax, and one of these animals died on the ninth day.

#### COMMENT

We shall not refer extensively to the literature on the use of pneumothorax in lobar pneumonia. The paper on the experimental work of Lieberman and Leopold<sup>2</sup> and the clinical report of Behrend and Cowper<sup>3</sup> contain a complete bibliography on the history of this subject.

Lieberman and Leopold<sup>2</sup> induced lobar pneumonia in dogs by modification of a method which we first devised,<sup>4</sup> that is, by the injection of a suspension of sedimented pneumococci into the lung with the aid of bronchoscopic observation. For anesthesia they used morphine (6 mg per kilogram of body weight) subcutaneously and sodium amytal (15 mg per kilogram) intraperitoneally. We have not found starch broth necessary for the production of pneumonia. What is more, in the present experiment we used much larger doses than are necessary to induce pneumonia, i e., at least 20 cc of broth culture (0.05 cc of sedimented organisms) for a dog weighing 10 Kg. This was done to obtain a series of animals comparable to that of Lieberman and Leopold. In a study on elasticity of the lung, shortly to be published, we regularly produced pneumonia by the insufflation of only 0.5 to 1 cc of a broth culture of pneumococcus, i e., with only one twentieth to one fortieth of the doses used in the present study.

The reader will recall the significant parallelism between pneumococcic bacteremia and the mortality, regardless of whether pneumothorax was used. That pneumothorax was of little or no therapeutic value in our experiments appears to be definite, but the close correlation between bacteremia and mortality is significant. We believe that this correlation exists in the data of Lieberman and Leopold and that in their experiments as well as in ours recovery had much more relation to the absence of

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3 Behrend, A., and Cowper, R. B. G. Artificial Pneumothorax in the Treatment of Lobar Pneumonia, *J. A. M. A.* **102** 1907 (June 9) 1934.

4 Coryllos, P. N., and Birnbaum, G. L. Lobar Pneumonia Considered as a Pneumococcic Massive Atelectasis of the Lung, *Bull. New York Acad. Med.* **4** 384 (March) 1928, footnote 1.

bacteremia than to the employment of pneumothorax (tables 2 to 5). For example, in table 2 of their paper<sup>1</sup> (page 320) it is shown that of fifteen dogs given pneumothorax that recovered, six, or 40 per cent, had bacteremia. On the other hand, in table 4 (page 328) it is pointed out that of the thirteen dogs not receiving pneumothorax that died, nine, or over 69 per cent, had bacteremia. Of the five dogs in their series not receiving pneumothorax that lived (table 5, page 329) only one, or 20 per cent, had bacteremia. For the dogs treated with pneumothorax that died, blood cultures were negative in all three instances, but it would have been of interest to know whether the blood from the heart contained pneumococci at death.

We take objection to the inclusion in table 4 (page 328) in the paper of Lieberman and Leopold,<sup>2</sup> of the data on three untreated dogs dying in twenty-four, thirty-six and thirty-six hours after insufflation of culture into the lung. These dogs are obviously not comparable subjects to be used as controls for animals receiving pneumothorax, since pneumothorax was usually given at least forty-eight hours after insufflation of *Pneumococcus*. It is clear that the group of animals receiving pneumothorax were able to withstand the disease for at least forty-eight hours before pneumothorax was produced. Obviously, we must begin the experiment with dogs in a comparable stage, leaving several animals to be used as controls and starting treatment of others with pneumothorax, if the merit of pneumothorax as a therapeutic measure is to be determined.

The same authors found that the animals with positive blood cultures before the production of pneumothorax usually had negative blood cultures on the day after treatment with pneumothorax. Is it not possible that the disappearance of bacteremia can occur without the employment of pneumothorax? At any rate, it is difficult to see how pneumothorax could so further collapse or immobilize a consolidated lobe as to close the blood and lymph vessels and prevent or diminish bacteremia. On the contrary, it is not difficult to see why pneumothorax can be a dangerous method by facilitating immobilization, impairing drainage and favoring bronchial obstruction in the diseased and in the uninvolved lobes.

Concerning the rôle of bacteremia in the fatal outcome of pneumonia, we have repeatedly pointed out the dual problem that exists—local pulmonary infection with production of toxins and generalized infection or bacteremia. Therapeutics must aim at both infections. In the experimental data it was evident that the incidence of mortality was high in cases of bacteremia, whether pneumothorax was used or not. In line with this reasoning is the work of Cecil and his collabor-

rators and that of other authors,<sup>5</sup> who showed that the mortality rate was significantly reduced by serum therapy, especially in the cases of bacteremia

It would, of course, be difficult to state whether the bacteremia is the main factor in the mortality rate, or whether it indicates that toxins produced in the lungs are escaping through the blood and lymph capillaries of the lungs and are finding their way into the blood stream with a facility equal to that of the pneumococci. Perhaps both factors are at play. It is possible that a focus of sepsis arising from pneumococci other than the infection in the lung could account for the death after a considerable time of animals in which the lungs are normal with or without a positive culture of the blood from the heart. The fact remains that animals with bacteremia showed a much greater mortality than those without, regardless of whether pneumothorax was given. It is also noteworthy that serum therapy in cases of pneumonia in man has significantly reduced the mortality rate only in the cases of bacteremia.

Reference will now be made to one of the latest clinical investigations of pneumothorax therapy in pneumonia, the study of Behrend and Cowper.<sup>3</sup> There are many points in the section of their paper entitled "Theoretical Aspects" which are worthy of comment. We agree with them that "all deaths from lobar pneumonia are due directly or indirectly

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5 Cecil, R. L., Baldwin, H. S., and Larsen, N. P. Lobar Pneumonia. A Clinical and Bacteriologic Study of Two Thousand Typed Cases, *Arch Int Med* **40** 253 (Sept.) 1932. Trask, J. D., O'Donovan, C., Jr., Moore, D. M., and Beebe, A. R. Studies on Pneumonia in Children. I. Mortality, Blood Cultures and Humoral Antibodies in Pneumococcus Pneumonia, *J Clin Investigation* **8** 623 (June) 1930. Ettinger, G. G., Masel, I., and Wiktorow, L. Zur Klinik und Epidemiologie der croupösen Pneumonie. I. Klinischer Verlauf und Pneumokokkentypen, *Deutsches Arch f klin Med* **174** 602, 1933. Cole, Rufus. Serum Treatment in Type I Lobar Pneumonia, *J A M A* **93** 741 (Sept 7) 1929. Cecil, R. L., and Plummer, Norman. Pneumococcus Type I Pneumonia. A Study of 1,161 Cases, with Especial Reference to Serum Therapy, *ibid* **95** 1547 (Nov 22) 1930. Quincke, H. Klinische Erfahrungen bei der Serumbehandlung der Pneumonie, *Ergebn d inn Med u Kinderh* **44** 655, 1932. Bullowa, J. G. M. Studies on the Serum Treatment of Pneumonia, *New York State J Med* **33** 13 (Jan) 1933. Suthff, W. D., and Finland, Maxwell. Type I Pneumococcic Infections with Especial Reference to Serum Treatment, *New England J Med* **210** 237 (Feb 1) 1934. Kereszturi, C., and Hauptman, D. The Serum Treatment of Pneumonia in Children, *J Pediat* **4** 331 (March) 1934. Avery, O. T., Chickering, H. T., Cole, Rufus, and Dochez, A. R. Acute Lobar Pneumonia. Prevention and Serum Treatment, Monograph 7, Rockefeller Institute for Medical Research, 1917. Gundel, B. Die Bakteriologie, Epidemiologie und spezifische Therapie der Pneumokokkeninfektionen des Menschen unter besonderer Berücksichtigung der Pneumonie, *Ergebn d Hyg, Bakt, Immunitätsforsch u exper Therap* **12** 131, 1931.

to toxemia ' On other points we disagree, such as, for example, the following (page 1907)

When acute inflammation occurs in a part of the body that is functionally or anatomically movable, experience has taught that the primary treatment of the affected part is rest We may cite, for example, the splinting of the joint in acute arthritides, the immobilization of the extremities in cellulitis and the strapping of the chest in pleurisy The object is to supplement by mechanical means the rational demands of the organism for rest

Lobar pneumonia furnishes an excellent example of acute inflammation in an organ whose function requires almost constant movement Attempts of the body to limit motion of the lung by decreased expansion and shallow frequent respirations cannot be too successful The introduction of air into the pleural cavity by artificial pneumothorax furnishes a mechanical aid that admirably accomplishes the desired results

When acutely inflamed pleural surfaces are separated, the pain formerly caused by every respiratory excursion disappears

We have repeatedly emphasized the part played by stagnation of secretion or exudate in the bronchi, bronchial obstruction and absorption of air in the pathogenesis of lobar pneumonia<sup>6</sup> As the affected lobe shrinks and exudate accumulates, re-aeration or expulsion of secretions by respiration and cough becomes increasingly difficult if not impossible For this reason even temporary accumulations of secretion and exudate in or obstructing the bronchus of a lobe may initiate pneumonic consolidation of the lobe which may not begin to clear before seven, eight or nine days when liquefaction of the fibinous exudate allows gradual ingress of air into and re-aeration of the lobe ("crisis") The comparison with acutely infected joints is not well taken, because experience in the World War has definitely proved that a septic joint needs drainage and not immobilization In tuberculous joints immobilization acts by decreasing the degree of hematosis and oxygenation of tissues, which is a different mechanism Therefore, rest of a lobe harboring pyogenic organisms and secretions is the last thing to be desired if bronchial obstruction, atelectasis and pneumonitis are to be avoided In the pathogenesis of pneumonia, bronchial obstruction, absorption of air, shrinkage of the lung and exudation go hand in hand We have shown<sup>1</sup> that *in vitro* pneumococci grow more profusely with a partial reduction of oxygen and that *in vivo* relatively small doses of pneumococci introduced below a mechanical obstruction of the bronchi produced very toxic pneumonia

It is not difficult to visualize the mechanism by which pneumothorax could relieve pleural pain by separation of the visceral pleura of a con-

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6 Coryllos, P. N., and Birnbaum, G. L. Bronchial Obstruction Its Relation to Atelectasis, Bronchopneumonia and Lobar Pneumonia a Roentgenographic Experimental and Clinical Study, *Am J Roentgenol* **22** 401, 1929

solidated lobe from the parietal. It is also possible that pneumothorax may, as occasionally it does in rare cases of bronchiectasis, facilitate drainage of the bronchi, however, it is reasonable to believe that the reverse occurs.

Behrend and Cowper<sup>3</sup> pointed to numerous reports of studies in the literature showing that pneumothorax causes a decreased circulation of blood and lymph in the capillaries of the lung. We agree with these views, our own work showing a decreased circulation of blood in the atelectatic or pneumonic lung. We agree that "lymph stasis with diminution of absorption of toxins has long been held largely responsible for the beneficent effect of artificial pneumothorax in pulmonary tuberculosis by Riviere, Warnecke, Mariotte, Gardner and others." We disagree with the statement "It doubtless functions in a similar manner in lobar pneumonia."

The statement that pneumothorax functions in a similar manner in lobar pneumonia and in tuberculosis is not warranted. In pneumonia pneumothorax is theoretically a threefold evil. It may collapse healthy tissue of the lung and thus hinder respiration, it may facilitate bronchial obstruction and thus induce pneumonia in a healthy or a partially affected lung, and it may hinder reexpansion of the pneumonic lung.

Is one to be forced to believe that a consolidated pneumonic lobe can be collapsed by the use of pneumothorax? Theoretically, however, a lobe with an early stage of pneumonia which is partially collapsed and the capillaries of which are still patent could be affected by pneumothorax through a diminished flow of blood and lymph, but pneumothorax, by hindering re-aeration and facilitating stagnation of exudates and obstruction of the bronchi, would tend to further the pneumonic process. Therefore, again, is one to believe that in an early stage of lobar pneumonia collapse therapy is rational and that attempts to improve the respiration of a lobe by hyperventilation, drainage by means of bronchoscopy<sup>7</sup> or any other method are irrational? Patency of the bronchi and alveolar ventilation are the best defense of the lung against infection which it resists in spite of the presence of numerous organisms in the bronchial tree.

The process of recovery in lobar pneumonia we believe, starts when the fibrinous exudate becomes sufficiently liquid, through the action of proteolytic ferments of the white cells to allow ingress of air and re-aeration of the lung. Likewise, we believe that in the early stage of lobar pneumonia, before "fixation" of the alveoli by fibrinous exudate every means should be utilized to encourage respiration of the lobe and to pre-

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7 Corvillos, P. N. Bronchoscopic Findings in Lobar Pneumonia, *Am J M Sc* **178** 8, 1929

vent or relieve obstruction of the bronchi, with the possible evil train of pathologic changes. For these reasons, we are opposed to the use of pneumothorax in lobar pneumonia, in either the early or the late stage. On the contrary, we are heartily in favor of collapse therapy with pneumothorax in tuberculosis, for in this condition compression, rest and atelectasis of a lobe are detrimental to the growth of the tubercle bacillus which is strictly an aerobe. The mechanism of cure and therapy in tuberculosis, as pointed out by one of us (P. N. C.),<sup>8</sup> is thus very different from that in lobar pneumonia. The rational therapy in lobar pneumonia and in pulmonary tuberculosis are diametrically opposed.

Behrend and Cowper reported the clinical relief of pain, toxicity, fever and cyanosis by the use of pneumothorax. They stated<sup>3</sup> (page 1,908) that with pneumothorax therapy the "cough is diminished and the amount of sputum becomes almost negligible." Diminution of cough and expectoration, we believe, is a distinct danger through facilitating bronchial obstruction in healthy lobes and hindering the re-aeration of a pneumonic lobe. We agree with their statement that the spread of the pneumococcal process to the opposite side "may constitute a real danger in the use of this form of therapy." Lastly, it is of interest that in the eleven cases which these authors reported the only two patients who died had had a positive blood culture, again a corroboration of the conclusion based on our experimental work that there is a close connection between bacteremia and mortality in lobar pneumonia.

In a protean disease like pneumonia it is dangerous to arrive at hasty conclusions based on a limited number of cases. The consensus as to the real usefulness of serum treatment even in pneumonia due to type I *Pneumococcus* is far from unanimous, notwithstanding the extensive statistics now available in the literature. A careful and impartial analysis of these statistics shows that the mortality in cases of pneumonia uncomplicated by bacteremia has been influenced little if any by the use of serum and that in cases with bacteremia, in which serum is more efficient, the mortality when treatment is given still varies widely in different years and in different localities. It is our opinion that serum injected into the circulating blood may influence bacteremia but that it is without marked action on the pulmonary focus, because little blood circulates in the consolidated and atelectatic pneumonic lung.

The pathogenesis and pathologic physiology and bacteriology of lobar pneumonia point to the rapid liberation and drainage of the obstructed bronchi and the re-aeration of the lung as the only logical treatment. The results obtained by one of us (P. N. C.) with drainage by means of

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8 Coryllos, P. N. Wie fuhren Ruhe- und Kollapsbehandlung zur Heilung der Lungentuberkulose? Deutsche Ztschr. f. Chir. **243** 701, 1934, Ueber die Bedeutung der Atelektase fur den Verlauf der Lungentuberkulose, Beitr. z. Klin. d. Tuberk. **85** 339, 1934.

bronchoscopy in cases of severe lobar pneumonia is in favor of this conception

In support of our opinion we shall briefly report here an instance of "miraculous success" obtained by pneumothorax in a patient with severe lobar pneumonia, referred by Dr. Malavazos, of Newark, to one of us (P. N. C.)

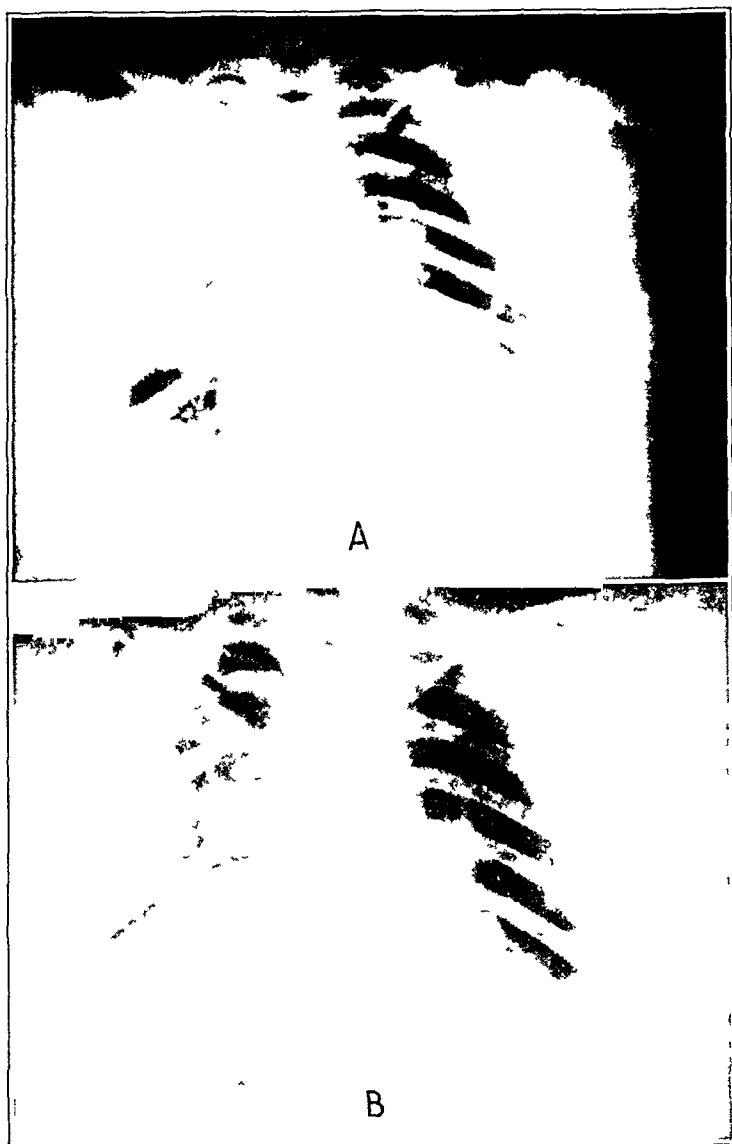


Fig 5—Roentgenograms of the chest of C. P., showing (A) pneumonia of the upper and middle lobes of the right lung and (B) the appearance forty-eight hours after the production of pneumothorax on the right side with 150 cc of air

#### REPORT OF CASE

C. P., a white woman aged 32, had an onset of pneumonia on May 3, 1934, with prolonged chill and pain in the right side of the chest. The physical examination on May 6 revealed a temperature of 104 F, a pulse rate of 135 and consolidation of the upper lobe of the right lung. On that day she was admitted to the Beth Israel Hospital in Newark, N. J. The blood examination on May 7



showed white cells 18,500, polymorphonuclears 60 per cent, stab forms from 2 to 4 per cent and lymphocytes 13 per cent. On May 8 the blood culture was positive for *Pneumococcus* type V. Twenty thousand units of polyvalent serum was administered in the course of twenty-four hours (on May 8). The temperature decreased from 105 to 101 F, and diaphoresis was profuse. However, a few hours later the temperature increased to 105.6 F, and examination showed extension of consolidation to the middle and upper lobes of the right lung, as shown in the roentgenogram (fig 5A). During the next three days (from May 9 to May 12) the temperature remained between 104 and 106 F, reaching the highest

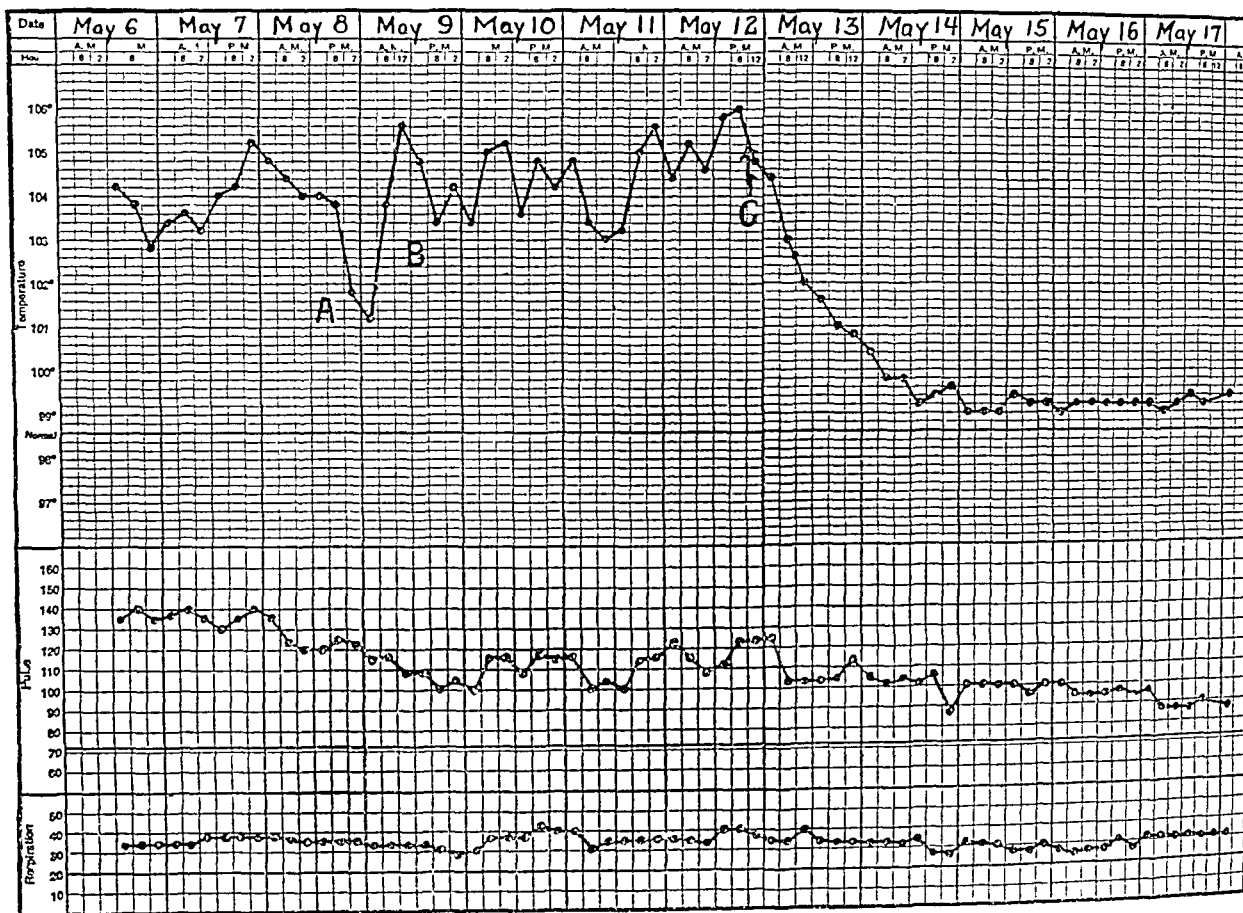


Fig 6—Clinical chart for the patient, roentgenograms of whose chest are shown in figure 5, indicating (A) the crisis of the initial process, (B) the beginning of the secondary process and (C) the point at which artificial pneumothorax was produced

point at 8 p m, May 12. At 11 p m of that day artificial pneumothorax was produced by one of us (P. N. C.), 150 cc of air being injected into the right pleural cavity.

Are we to attribute this success to pneumothorax? We do not believe that we should. In this case the course of recovery was strikingly similar to that in postoperative atelectasis, namely, productive cough, profuse expectoration and rapid decrease in temperature by crisis. In

other words, liberation of the obstructed bronchi and drainage of the pulmonary foci are effected as is drainage in cases of abscess of the lung or of any other organ or part of the body. The introduction of 150 cc of air cannot reasonably produce such an effect and with such lightning speed. The only reasonable explanation of the success of the use of pneumothorax in this case is that it was applied at the opportune moment when the crisis was about to occur.

From consideration of the experimental and clinical data we believe that we can conclude that pneumothorax has no real therapeutic effect in pneumonia.

#### SUMMARY AND CONCLUSIONS

In a group of forty dogs with experimentally induced lobar pneumonia the effects of artificial pneumothorax as a therapeutic measure were studied. Various analyses of the data were also made from the standpoint of the incidence of toxicity, bacteremia and mortality.

It was found that the mortality rate closely paralleled the incidence of bacteremia, regardless of whether pneumothorax was used. Pneumothorax was found ineffective for the relief of clinical symptoms or for reduction of the mortality rate.

The theoretical disadvantages of pneumothorax were pointed out. The dual infectious nature of the disease was emphasized, namely, the local pulmonary infection and the generalized bacteremia. Caution was urged in the evaluation of the clinical merit of pneumothorax in lobar pneumonia.

The facts in a case of lobar pneumonia in man, occurring in our personal experience, in which pneumothorax was followed by crisis within twenty-four hours were analyzed, and the relation of pneumothorax to this "miraculous cure" was discussed.

It is our opinion that artificial pneumothorax may relieve pleuritic pain but that it does not influence the crisis in lobar pneumonia.

# Progress in Internal Medicine

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## BRIGHT'S DISEASE A REVIEW OF RECENT LITERATURE

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As in the previous review written one year ago, I make no attempt to include all of the numerous articles which have appeared in this field but merely review some of those which most clearly indicate the present trend of thought and those which mark new advances in the frontier of knowledge

### GLOMERULONEPHRITIS

Concerning the etiology of diffuse glomerulonephritis, some of the most important work of the last decade is that of Longcope and his associates, an initial report of which appeared in 1927<sup>1</sup> The sequel to this work has recently been reported by Winkenweider, McLeod and Baker,<sup>2</sup> who have made an analysis of the associated infections in 78 cases of hemorrhagic nephritis, 40 of which were included in the original report of Longcope in 1927 Thus it becomes possible now to give a better evaluation of the work of the Longcope school than would have been the case a year ago

Winkenweider, McLeod and Baker - present even stronger evidence than was given in the first report of the close relationship between infection with *Streptococcus haemolyticus* and glomerular nephritis Infection of the upper respiratory tract with the beta type of this organism precedes the nephritis in the great majority of cases The alpha type is apparently responsible for a small number of cases When the onset of nephritis is preceded by acute infection, there is apparent a greater tendency to healing or to latency as a sequel than when the onset is preceded by a chronic infection, which seems to favor persistence of the infection and a chronic progressive type of nephritis In 10 or 12 per cent of the cases no connection with streptococcic

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1 Longcope, W T , O'Brien, D P , McGuire, J , Hansen, O C , and Denny, E R Relationship of Acute Infections to Glomerular Nephritis, *J Clin Investigation* 5 7, 1927

2 Winkenwerder, W L , McLeod, N , and Baker, M Infection and Hemorrhagic Nephritis, *Arch Int Med* 56 297 (Aug ) 1935

infection was proved. There was no evidence that pneumococcic pneumonia, rheumatic fever or syphilis had any causal relationship to the nephritis.

Seasonal variations in the frequency of hemorrhagic nephritis corresponded with those of respiratory infection in Baltimore. The prodromal period between the onset of infection and the appearance of nephritis was from three to twenty-eight days, most frequently seven days, with an average length of ten and nine-tenths days. This period is somewhat shorter than previous reports would indicate.

Exacerbations of nephritis are usually due to streptococcic infection of the respiratory tract and are commonest in the latent and progressive forms of nephritis, though exacerbation may be induced by surgical procedure. The prodromal period between infection and exacerbation is short, from twenty-four to forty-eight hours. When streptococcic infection occurred during convalescence from nephritis it did not prevent recovery, and after recovery was established it rarely caused a relapse. Most characteristic of the progressive types of nephritis was a "carrier state" without recurring evidences of active infection. The character of the causal infection seems to determine the outcome of hemorrhagic nephritis. Acute reactions to infection predispose to recovery. Chronic infection in which the resistive reactions are incomplete and the organisms persist result in a chronic progressive nephritis.

Attempts to produce a chronic progressive diffuse hemorrhagic nephritis have almost universally failed, no doubt because chronic streptococcic infections are difficult to establish in animals. In 1931 Lukens and Longcope<sup>3</sup> were able to produce acute diffuse glomerulitis, and by a variety of methods other workers have been able to effect somewhat similar results. One of the most recent attempts is that of Vallery-Radot, Dérot and Gauthier-Villars,<sup>4</sup> who produced glomerular lesions by the injection into rabbits of filtrates of cultures of virulent streptococci. There developed serous effusions, azotemia and albuminuria. No mention is made of the occurrence of hematuria in these animals. Histologically, in addition to glomerulitis, there were a few tubular and some interstitial changes, but nothing resembling chronic glomerular nephritis was produced.

In the French literature there is recurring reference to the problem of the "waï nephritis." Celice and Albeaux-Fernet<sup>5</sup> report a case of

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3 Lukens, F. D. W., and Longcope, W. T. Experimental Acute Glomerulitis, *J. Exper. Med.* **53** 511, 1931.

4 Vallery-Radot, P., Dérot, M., and Gauthier-Villars, P. Nephrites expérimentales obtenues par l'injection au lapin de filtrats streptococciques, *Ann. de med.* **38** 100 (June) 1935.

5 Celice, J., and Albeaux-Fernet, M. Forme rénale pure de spirochétose, *Ann. de med.* **38** 70, 1935.

infection with a spirochete, without jaundice, but characterized by acute nephritis of a type commonly observed during the World War. In 11 of Winkenwerder's<sup>2</sup> series of 78 cases of hemorrhagic nephritis no relation to streptococcic infection could be discovered. One wonders what proportion of the cases without streptococcic infection may be of spirochetal origin.

Seegal, Seegal and Lyttle<sup>6</sup> have analyzed the data concerning the infections preceding acute hemorrhagic nephritis in the histories of 379 cases. The results agree with those of the Longcope-Winkenwerder series quite well. In the majority of cases the preceding infection was a deep streptococcic infection, such as cervical lymphadenitis, peritonsillar abscess, otitis media or mastoiditis. Scarlet fever played a relatively minor rôle. In a small percentage of cases the nephritis was preceded by pneumococcic pneumonia or an infection with *Staphylococcus*, and in a few cases it was preceded by a fever of unknown origin. Other points of interest in their observations were the facts that 50 per cent of the cases occurred in persons under the age of 10 years and 70 per cent in persons under 20 and that the incidence in males predominated over that in females in a ratio of 2:1.

In another paper Seegal, Seegal and Jost<sup>7</sup> compared the incidence of scarlet fever, acute rheumatic fever and acute nephritis at different latitudes in the United States. Scarlet fever and rheumatic fever are apparently much more prevalent in the northern latitudes, while the incidence of acute nephritis is nearly as high in southern as in northern latitudes.

A new contribution to the pathologic histology of glomerulonephritis has been made by MacCallum,<sup>8</sup> who reviewed the glomerular changes observed in the last 5,000 autopsies at the Johns Hopkins Hospital by means of a special staining technic. He noted that the capillaries of the glomerulus stand in the same relation to the epithelium of the glomerulus as the capillaries of the tubules do to the epithelium of the tubules. This suggests to MacCallum that the epithelium must govern the functions of the glomerulus. He observed that the basement membrane is separated from the wall of the capillaries and that connective tissue between the capillaries is to be found in the glomerular tufts. Various injuries result in reparative processes which produce much new con-

6 Seegal, D., Seegal, B. C., and Lyttle, J. D. The Nature of the Preceding Infection in Acute Glomerulonephritis in Two New York Hospitals and in Four Southern Hospitals, *J. A. M. A.* **105** 17 (July 6) 1935.

7 Seegal, D., Seegal, B. C., and Jost, E. L. Geographic Distribution of Rheumatic Fever, Scarlet Fever and Acute Glomerulonephritis in North America, *Am. J. M. Sc.* **190** 383 (Sept.) 1935.

8 MacCallum, W. G. Glomerular Changes in Nephritis, *Bull. Johns Hopkins Hosp.* **55** 416, 1934.

nective tissue between the capillaries, displacing and compressing them. In some instances this may be associated with a great proliferation of epithelium. MacCallum could find no case in which endothelial proliferation led to the obstruction of capillaries, so that he prefers to speak of "intercapillary" rather than "intracapillary" glomerulonephritis. When amyloid occurred it was found between the basement membrane and the capillary.

Another interesting morphologic study is that of Oliver and Luey,<sup>9</sup> who have discovered aglomerular tubules in contracted kidneys of certain persons with glomerulonephritis. In some instances a tubule may survive the complete occlusion of its glomerulus, owing to the continued patency of the vessel of Ludwig, which makes a direct communication between the afferent arteriole and the capillaries of the tubules. Oliver and Luey speculate somewhat on the possibilities of function in these surviving tubules on the basis of analogies in fish with aglomerular nephrons.

#### DEGENERATIVE FORMS OF BRIGHT'S DISEASE

In the previous review of this subject attention was drawn to the growing tendency to cast doubt on the existence of a true pure lipid nephrosis as distinct from the nephrotic type of chronic glomerulonephritis. In the past year this tendency has received further impetus. Vallery-Radot, Delafontaine and Trombert<sup>10</sup> report some cases which were supposed to have been examples of true lipid nephrosis in which the condition subsequently became uremic. These authors believe that this occurrence is not infrequent if the cases of so-called nephrosis are followed for a sufficiently long time.

Blackman<sup>11</sup> reports on the anatomic findings in cases of the classic syndrome of lipid nephrosis which proved at autopsy to be instances of diffuse glomerulonephritis. The same author studied the forms of nephritis which were produced experimentally by means of a pneumococcus toxin<sup>12</sup>. He observed that the quantity of toxin given and the degree of immunity which develops are the important factors in determining the histologic lesions produced in the kidneys as well as the

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9 Oliver, J, and Luey, A. S. Plastic Studies in Abnormal Renal Architecture. III. The Aglomerular Nephrons of Terminal Hemorrhagic Bright's Disease, *Arch. Path.* **19** 1 (Jan.) 1935.

10 Vallery-Radot, P., Delafontaine, P., and Trombert, J. L'évolution de la "nephrose lipidique" vers l'azotémie, *Ann. de méd.* **38** 79 (June) 1935.

11 Blackman, S. S. Pneumococcal Lipoid Nephrosis and the Relation Between Nephrosis and Nephritis. I. Clinical and Anatomical Studies, *Bull. Johns Hopkins Hosp.* **55** 1, 1934.

12 Blackman, S. S. Pneumococcal Lipoid Nephrosis and the Relation Between Nephrosis and Nephritis. II. Experimental Studies, *Bull. Johns Hopkins Hosp.* **55** 85, 1934.

clinical manifestations of these forms. From his work it would appear that predominance of degenerative change is noted when immunity to the toxin is low and that the features of progressive glomerulonephritis begin to appear as the immunity increases. Blackman's conception of the process of glomerulitis seems to follow that of MacCallum.<sup>8</sup> When immunity is high the process of healing takes place, and this is characterized by intercapillary fibrosis resulting in progressive obliteration and excessive regeneration of epithelium. He finds the chief anatomic distinction between nephrosis and glomerulonephritis to be the absence of coagula containing fibrin within the glomeruli in the former. In the absence of these, organization and formation of scar tissue do not occur.

Blackman's views on the pathogenesis of lipid nephrosis and glomerulonephrosis<sup>13</sup> are stimulating and important. The papers may be criticized for a style suggestively polemic, so that their objectivity is slightly marred by the impression of special pleading.

The occasional association of renal degeneration with the excretion of Bence-Jones protein is well known. Forbus, Perlzweig, Parfentjev and Burwell<sup>14</sup> have investigated the problem experimentally. In a case in man the excretion of large amounts of this protein led to its precipitation in the tubules, with the formation of peculiar casts. When these completely obstructed a tubule a foreign body reaction resulted in extensive secondary changes in the nephron, leading to its destruction and fibrous replacement. Although the kidneys of certain animals are permeable to Bence-Jones' protein, its administration in large amounts over a period of days did not produce injury detectable by the microscope. In one dog a few isolated lesions resembling those in man were produced. Failure to reproduce the picture presented by the human patient may have been due to insufficient time or to the absence of the special conditions which led to the precipitation of the protein in the tubules.

The question of an optimal diet for promoting the gain of nitrogen in cases of nephrosis is discussed by Liu and Chu.<sup>15</sup> The authors report observations on 2 patients with the nephrotic syndrome. One of the patients had microscopic hematuria (presumably glomerulonephritis), and the other had syphilis but did not have demonstrable hematuria. Optimal gains of nitrogen occurred when the dietary protein furnished from 12 to 13 per cent of the total number of calories. The authors

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13 Blackman, S. S. On the Pathogenesis of Lipoid Nephrosis and Progressive Glomerulonephritis, *Bull. Johns Hopkins Hosp.* **57** 70, 1935.

14 Forbus, W. D., Perlzweig, W. A., Parfentjev, I. A., and Burwell, J. C. Bence-Jones Protein Excretion and Its Effects upon the Kidney, *Bull. Johns Hopkins Hosp.* **57** 47, 1935.

15 Liu, Shih-Hao, and Chu, Hsien-I. An Optimal Diet in Promoting Nitrogen Gain in Nephrosis, *J. Clin. Investigation* **14** 293 (May) 1935.

found that the positive nitrogen balance was not increased when a higher proportion of protein was given. In spite of the large amount of nitrogen gained the protein content of the plasma was relatively little affected. In the patient with hematuria the amount of plasma protein remained low and albuminuria continued unabated. In the patient without hematuria the albuminuria gradually diminished and the concentration of protein in the plasma increased.

Similar studies were made by Keutmann and Bassett,<sup>16</sup> who studied 3 patients in the nephrotic stage of glomerulonephritis. Two of these patients failed to show an increase in the amount of circulating protein in spite of an enormous deposition of nitrogen in their bodies. The third patient slowly improved.

The observations of Keutmann and Bassett<sup>16</sup> show that there is no lack of ability in the nephrotic person to synthesize new protein. The amount synthesized was calculated as the sum of protein stored and protein in the urine. By a comparison of observations made during periods with the patient on a basic diet with those made in alternating periods during which specific supplements were added, an attempt was made to determine the degree of utilization of the supplements, which consisted of egg white, lactalbumin and protein of liver residue. When the intake of protein was increased the amount of protein in the urine usually increased, an effect which the authors attribute to an increased perfusion of the kidneys.

From the results reported in these two papers by Keutmann and Bassett it is clear that the nephrotic state does not involve a failure of regenerative synthesis of protein. It is also clear that an increase in the amount of circulating proteins of the plasma can be effected only through the mechanisms which increase the ability of the capillary membranes to retain them, that is, through a decrease in permeability.

Yanagi<sup>17</sup> has made some interesting observations on the stability of the protein in the plasma as indicated by the length of time during which the maximum pressure which is developed in an osmometer is maintained. The maximum pressure developed by a normal amount of protein in the serum is maintained from sixteen to eighteen hours. In serums with a low concentration of protein the pressure rose to a maximum in from three to five hours, after which a gradual decrease occurred. This reduced stability could be reproduced experimentally by dilution of normal serum with physiologic solution of sodium

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<sup>16</sup> Keutmann, E. H., and Bassett, S. H. Dietary Protein in Hemorrhagic Bright's Disease. II. The Effect of Diet on Serum Proteins, Proteinuria and Tissue Protein, *J Clin Investigation* **14** 871 (Nov.) 1935.

<sup>17</sup> Yanagi, K. A Clinical and Experimental Study of the Colloid Osmotic Pressure of Serum Protein, *J Clin Investigation* **14** 853 (Nov.) 1935.



chloride or with an ultrafiltrate from normal serum. If serum with a low concentration of protein was concentrated to 6 per cent by ultrafiltration the curve of the osmotic pressure resembled that of normal serum.

For a number of years Grabfield and his co-workers have been concerned with the nature of "deposit protein." The problem has been approached by a study of the differences in the excretion of nitrogen and of sulfur produced by the exhibition of iodides and salicylates in normal and nephritic subjects. A tendency for the edematous subject to retain sulfur in excess of nitrogen has been noted. Grabfield and Adams<sup>18</sup> reported experiments in which diets low in sulfur were given to 7 patients, 3 of whom had a normal concentration of protein in the serum and 4 of whom had a low concentration. On such diets the nephrotic patients excreted less sulfur than did those whose concentration of protein was normal. The authors wisely refrain from trying to explain the phenomenon at this time. However, the accumulating data may ultimately throw some light on the nature of "deposit protein."

In the treatment of edema in persons with nephrosis attempts have been made to increase the colloid osmotic pressure of the blood plasma by the injection of solutions of acacia. Dick, Warweg and Andersch<sup>19</sup> report experiences with this procedure which indicate that it is not only futile but harmful. Acacia was subsequently found in edema fluids and in appreciable amounts in the liver and other organs and tissues. It was noted that these changes were accompanied by a further decrease in the protein content of the serum. In view of such experience the further use of acacia seems to be unwarranted.

#### NEPHRITIS AND THE TOXEMIAS OF PREGNANCY

Herrick and Tillman<sup>20</sup> contribute a valuable study in recording the results of a prolonged period of observation of 594 women with toxemia of pregnancy. The observations, which ranged in duration from one to twenty-two years, with an average of five and six-tenths years, revealed the startling fact that more than one half of the survivors of the condition were found to have symptoms and signs of either glomerulonephritis or hypertensive cardiovascular disease within a period of three years.

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18 Grabfield, G. P., and Adams, L. G. Nitrogen and Sulphur Metabolism in Bright's Disease. VI. Effect of Diets Low in Sulphur on the Excretion of Sulphur, *Arch Int Med* **55** 360 (March) 1935.

19 Dick, M. W., Warweg, E., and Andersch, M. Acacia in the Treatment of Nephrosis, *J A M A* **105** 654 (Aug 31) 1935.

20 Herrick, W. W., and Tillman, A. J. B. Toxemia of Pregnancy. Its Relation to Cardiovascular and Renal Disease, *Arch Int Med* **55** 643 (April) 1935.

In 11 cases an autopsy was performed, the anatomic diagnosis of chronic glomerulonephritis was made in 4 cases and that of cardiovascular disease with hypertension in 7. The clinical as well as the pathologic evidence suggests a continuous chain of events in the cases with cardiovascular sequelae in which the injury of the acute phase fails to heal and hyperpiesis becomes permanent. In women with glomerulonephritis, whether latent or manifest, pregnancy activates the disease and aggravates it roughly in proportion to the size of the fetus. In such women repeated pregnancies encroach further on the factor of safety of the kidney and should be avoided.

In making a differential diagnosis between the types of toxemia occurring during pregnancy the Addis count of the urinary sediment will probably assume increasing importance. In this connection one is indebted to Elden and Cooney<sup>21</sup> for a study of urinary sediments and of the urea clearance in women during the last trimester of a normal pregnancy. In 19 normal women the cast count ranged from 0 to 10,000, the erythrocyte count from 47,000 to 1,900,000 and the count for epithelial cells and leukocytes from 25,000 to 6,000,000 per twelve hour night specimen. The urea clearance varied from 60 to 118 per cent of the average normal standard clearance. Nice<sup>22</sup> has also studied the urea clearance during normal pregnancy, observing that the mean value ante partum was 153 per cent, that the mean value post partum was 95.5 per cent and that the mean value for nonpregnant normal women was 105 per cent of the standard clearance values of Van Slyke.

Harvey Cushing<sup>23</sup> reports the finding of pronounced basophilic invasion of the neurohypophysis in 6 fatal cases of eclampsia of pregnancy. There were 3 other cases in which this finding was less definite. Cushing believes that this is the histopathologic basis of eclampsia and of some types of primary hypertension of young people.

Thus it appears that the renal lesions of the toxemias of pregnancy are coming to be thought of as separate entities. Certainly Herrick and Tillman have shown that a substantial number of them belong to the realm of glomerulonephritis and the remainder to that of the vascular nephropathies. The usefulness of the term nephrosis of pregnancy is doubtful.

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21 Elden, C. A., and Cooney, J. W. The Addis Sediment Count and Blood Urea Clearance Test in Normal Pregnant Women, *J. Clin. Investigation* **14** 889 (Nov.) 1935.

22 Nice, M. Kidney Function During Normal Pregnancy. I. The Increased Urea Clearance of Normal Pregnancy, *J. Clin. Investigation* **14** 575 (Sept.) 1935.

23 Cushing, H. Hyperactivation of the Neurohypophysis as the Pathological Basis of Eclampsia and Other Hypertensive States, *Am. J. Path.* **10** 145, 1934.

ARTERIOSCLEROTIC FORMS OF BRIGHT'S DISEASE—THE  
NEPHROSCLEROSSES

There has been for some time a widespread appreciation of the existence of two types of essential hypertension, expressed in the Geiman conception of the "red" and the "pale" type or in current usage benign and malignant. The conception of malignant hypertension as a nosologic entity is still somewhat confused, though much has been done to establish histologic differentiations between the arteriolar changes in the benign and those in the malignant forms and to distinguish between the glomerular changes which characterize glomerulonephritis and malignant nephrosclerosis. Benign essential hypertension can and frequently does exhibit rather fulminating phenomena in its later stages, which tend to confuse some clinicians on the "malignancy" of the disease. A recent paper by MacMahon and Pratt<sup>24</sup> is timely in that it gives a general review of the anatomic and clinical phenomena which justify the nosologic differentiation of a malignant type of hypertension from the more common benign type.

MacMahon, Close and Hass<sup>25</sup> have made a careful anatomic study of the cardiovascular and renal lesions in 2 cases of basophilic adenoma of the pituitary. The lesions found corresponded closely with the picture originally described as malignant nephrosclerosis by Fahr. A similar case is reported by Close<sup>26</sup>. Ahlstrom<sup>27</sup> also describes the hypophyseal changes in 2 cases of malignant nephrosclerosis. In 1 case there was a small chromophobe adenoma in an apparently normal anterior lobe, with pronounced basophilic infiltration of the neurohypophysis. In a second case there was a cyst of the pars intermedia which was filled with a basophilic colloid material. There was also some infiltration of the posterior lobe by basophil cells. As one reviews these papers, the conviction grows that malignant nephrosclerosis is a distinct nosologic entity not to be confused with benign hypertension but closely related to eclampsia of pregnancy and to basophilia of the pituitary body.

In the field of treatment of hypertension there are two new developments of great interest. Page and Heuer<sup>28</sup> report the surgical section

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24 MacMahon, H. E., and Pratt, J. H. Malignant Nephrosclerosis (Malignant Hypertension), *Am J M Sc* **189** 221 (Feb) 1935

25 MacMahon, H. E., Close, H. G., and Hass, G. Cardiovascular Renal Changes Associated with Basophil Adenoma of the Anterior Lobe of the Pituitary (Cushing's Syndrome), *Am J Path* **10** 177, 1934

26 Close, H. G. Basophil Adenoma of the Pituitary Gland with Renal Changes, *Brit M J* **1** 356 (Feb 23) 1935

27 Ahlstrom, C. G. Hypophysial Changes in Malignant Nephrosclerosis, *Acta path et microbiol Scandnav* **12** 232, 1935

28 Page, I. H., and Heuer, G. J. A Surgical Treatment of Essential Hypertension, *J Clin Investigation* **14** 22 (Jan) 1935

of the anterior roots of the spinal nerves from the sixth thoracic to the second lumbar vertebra in a young girl with hypertension. As a result of this procedure the blood pressure quickly returned to normal, no change in the excretion of urea was noted, there was slight loss of power of concentration and no increase in hematuria. This operation of Page and Heuer is quite formidable, requiring a laminectomy and producing paralysis of the abdominal muscles. A second procedure has been tried by Peet,<sup>29</sup> who has published a preliminary report of section of the roots of the splanchnic nerves in the lower thoracic segments. Since this leaves the abdominal musculature intact and since it can be more easily carried out, a complete report will be awaited with great interest.

#### CONTRACTED KIDNEY DUE TO PYELITIS

Longcope and Winkenwerder<sup>30</sup> describe the clinical features of this condition, which is probably not very rare. It is more common in women, characterized by attacks of lumbar pain and sometimes of fever. It may be symptomless up to the uremic stage. Of 9 cases studied, death occurred in 5 of uremia, in 5 there was high blood pressure and in 4 there were pathologic changes in the retina. Progressive anemia and polyuria were common features. The pyelograms revealed irregularities of the pelvis and calices. The urine in such cases is of low specific gravity and contains little albumin and few casts. Erythrocytes were present in 1 case only, in which there were ulcers in the bladder. Impaired renal function often preceded death by years and often progressed before symptoms were noted. At autopsy the kidneys were small, scarred and uneven, with a distorted irregular dilated pelvis and varying degrees of inflammation. Between scars relatively normal renal structure was preserved.

#### CYSTIC DISEASE OF THE KIDNEYS

Bell<sup>31</sup> gives the incidence of this condition as 1 in each 500 autopsies. In from 5 to 10 per cent of the cases it is unilateral. He classifies the condition in two types: surgical, in which signs are referable to one kidney (pain, tumor, hematuria, infection, etc.), and medical, in which acute or chronic renal insufficiency with hypertension and cardiovascular changes is observed. Willer<sup>32</sup> discusses the relationship of cystic dis-

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29 Peet, M. M. Splanchnic Section for Hypertension. Preliminary Report, Univ. Hosp. Bull., Ann Arbor **1** 17 (June) 1935.

30 Longcope, W. T., and Winkenwerder, W. L. Clinical Features of the Contracted Kidney Due to Pyelonephritis, Bull. Johns Hopkins Hosp. **53** 255, 1933.

31 Bell, E. T. Cystic Disease of the Kidneys, Am. J. Path. **11** 373, 1935.

32 Willer, H. Ueber kongenitale Zystenmieren und Blutdruck, Munchen med. Wchnschr. **82** 1437 (Sept. 6) 1935.

ease and hypertension. He believes that their concurrence is a matter of chance and that the high blood pressure is not secondary to the loss of renal tissue.

#### RENAL DISEASE AND THE PARATHYROID GLANDS

Albright, Baird, Cope and Bloomberg<sup>33</sup> collected reports of 83 cases of hyperparathyroidism, in 43 of which some type of renal damage was observed. This was attributed to the precipitation of calcium in the tubules, with resultant sclerosis, contraction and insufficiency, or to the formation of calculi in the pelvis with associated pyelonephritis.

Thirty years ago MacCallum<sup>34</sup> reported the finding of a tumor of a parathyroid gland in a young woman who died of glomerulonephritis. The remaining parathyroid glands were normal. Two other cases of advanced chronic nephritis were studied from the standpoint of the parathyroid glands. In 1 case abundant mitoses were found in the glands, while in the other case none were to be seen. This led Pappenheimer and Wilens<sup>35</sup> to reinvestigate the question. They report that the weight of the parathyroid glands is related to age and sex in normal persons. Their data indicate clearly a considerable increase in the weight of the parathyroid glands in persons with advanced renal disease roughly proportional to the severity and extent of the lesions and to the intensity of the renal insufficiency. The functional significance of these changes is not wholly clear. It may be in some way compensatory for the disturbance in the excretion of inorganic phosphates in persons with renal insufficiency.

#### RENAL FUNCTION

The measurement of the urea clearance in children has been facilitated by the development of a micromethod for determination of the values for urea in the blood and an automatic collector of urine for use with infants. These have been described by Farr.<sup>36</sup> The determination of urea is made on as little as 0.25 cc. of blood.

Cullen, Nelson and Holmes<sup>37</sup> found the values for urea clearance of normal children to have a distribution and mean corresponding to those of normal adults. Observations were made on 78 children with

33 Albright, F., Baird, P. C., Cope, O., and Bloomberg, E. Studies on the Physiology of the Parathyroid Glands. Renal Complications of Hyperparathyroidism, *Am J M Sc* **187** 49, 1934.

34 MacCallum, W. G. Tumour of the Parathyroid Glands, *Bull Johns Hopkins Hosp* **16** 87, 1905.

35 Pappenheimer, A. M., and Wilens, S. L. Enlargement of the Parathyroid Glands in Renal Disease, *Am J Path* **11** 73, 1935.

36 Farr, L. E. A Micromethod for Blood Urea and an Automatic Urine Collector for Urea Clearance in Infants, *J Clin Investigation* **14** 911 (Nov) 1935.

37 Cullen, G. E., Nelson, W. E., and Holmes, P. E. Studies of Kidney Function in Children, *J Clin Investigation* **14** 563 (Sept) 1935.

a history of hemorrhagic nephritis, and in this group the distribution and means corresponded with those of the normal group. When clearances were measured during the acute stage of the nephritis lower values were noted, but as a rule they returned to normal within a month after cessation of the acute symptoms. These findings emphasize the generally favorable outcome of hemorrhagic nephritis in children and the relative rarity of persistent functional impairment.

Van Slyke, Page, Hiller and Kerk<sup>38</sup> have made a further contribution to the study of urea clearance by the discovery that in persons with acidosis the clearance values are low if they are calculated from the urea and that they are normal if calculated from the urea plus ammonia. The authors believe that this indicates that the urinary ammonia is formed at the expense of the urea removed from the blood. In the formula  $\frac{UV}{B}$  or  $\frac{UV\sqrt{V}}{B}$  the U should represent urea plus ammonia. The determination is simplified by the determination of the nitrogen content from reaction with an alkaline hypobromite. The routine procedure for this determination is described by Fair<sup>36</sup>.

MacKay and Rytand<sup>39</sup> made a statistical analysis of the relationship of the phenolsulfonphthalein test, the Addis ratio and the concentration of urea in the blood as a measure of the amount of functioning renal tissue in patients with Bright's disease. They state "For certain clinical purposes the Addis ratio may be predicted as a percent of normal from the blood urea by dividing 1,755 by the blood urea concentration and from the phenolsulfonphthalein test by multiplying the percentage of dye excreted by 1." They observed that the ratio can be more accurately predicted by the results of the dye test than by the concentration of the blood urea. It was also noted that the excretion of dye and the concentration of urea in the blood may be well within normal limits until at least half the normally functioning renal tissue has been destroyed. An observation of somewhat similar nature had previously been made by Van Slyke in a comparison of the excretion of phenolsulfonphthalein with urea clearance.

Mosenthal and Bruger<sup>40</sup> have studied the value of the ratio  $\frac{100 \times \text{urea nitrogen}}{\text{nonprotein nitrogen}}$  as an index of renal function, comparing it with Van Slyke's urea clearance, with which in general it agrees. Normal values are 44 or less, while with maximal impairment of function they exceed 80. The ratio rises and falls as function fails or improves.

38 Van Slyke, D. D., Page, I. H., Hiller, A., and Kirk, E. Studies of Urea Excretion. IX. Comparison of Urea, Plus Ammonia, and of Nitrogen Determinable by Hypobromite, *J. Clin. Investigation* **14**: 901 (Nov.) 1935.

39 MacKay, E. M., and Rytand, D. A. Significance of the Phenolsulfonphthalein Test of Renal Function, *Arch. Int. Med.* **55**: 131 (Jan.) 1935.

40 Mosenthal, H. O., and Bruger, M. The Urea Ratio as a Measure of Renal Function, *Arch. Int. Med.* **55**: 411 (March) 1935.

All types of renal disease have been studied. One wonders what values will be obtained in persons with severe hepatic disorders, in whom abnormal values for urea in the blood are sometimes noted. Apart from a few such questions it is anticipated that the Mosenthal-Bruger ratio may be very useful when only data on the chemistry of the blood are available, for instance, in cases in which the inability to collect urine renders determination of the urea clearance impossible.

Observations have been made by Page and Heuer<sup>41</sup> on the effect of renal denervation on arterial blood pressure and renal function in cases of essential hypertension. No effects on either were observed following bilateral denervation. Similar studies by these authors<sup>42</sup> were made on patients with nephritis. They found that denervation of the kidney, on one side as well as on both sides, caused a diminution in the amount of urinary protein in 4 of 5 cases of chronic nephritis. No changes in the urea clearance were noted following this procedure.

One of the outstanding papers of the year is that of Landis, Elsom, Bott and Shiels,<sup>43</sup> who draw attention to the important relation between sodium chloride and urea clearance in cases of severe renal insufficiency. These authors recall that in persons with intact kidneys in any of a number of shocklike states the chloride content of the plasma is low and the concentration of urea in the blood is high and that in such states the administration of sodium chloride raises the chloride content and lowers the urea content. The authors have noted also that in some cases of advanced renal insufficiency the administration of sodium chloride may have a similar effect when the chloride content is low. This is accomplished by slight increases in the urea clearance, which, though small, have a large cumulative effect in reducing azotemia. For instance, in 1 case the chloride content of the plasma was increased from 94 to 100 milliequivalents per liter, while the urea nitrogen content of the plasma fell from 154 to 32.8 mg, the creatinine content of the plasma fell from 7.2 to 5 mg and the phosphate content of the serum from 7.3 to 4.9 mg per hundred cubic centimeters. Landis also made use of a twelve or twenty-four hour specimen of urine for the determination of the urea clearance, because he found the values to vary less than in the one or two hour specimens usually employed. When these variations are eliminated it is possible to detect the small changes in function which the administration of sodium chloride effects.

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41 Page, I. H., and Heuer, G. J. The Effect of Renal Denervation on the Level of Arterial Blood Pressure and Renal Function in Essential Hypertension, *J Clin Investigation* **14** 27 (Jan) 1935.

42 Page, I. H., and Heuer, G. J. The Effect of Renal Denervation on Patients Suffering from Nephritis, *J Clin Investigation* **14** 443 (July) 1935.

43 Landis, E. M., Elsom, K. A., Bott, P. A., and Shiels, E. Observations on Sodium Chloride Restriction and Urea Clearance in Renal Insufficiency, *J Clin Investigation* **14** 525 (Sept) 1935.

## Book Reviews

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**Failure of the Circulation** By Tinsley R. Harrison, M.D., associate professor of medicine, Vanderbilt University School of Medicine Price, \$4.50 Pp 396, with 22 tables and 60 illustrations Baltimore William & Wilkins Company, 1935

In this rather short single volume Harrison has given the American medical profession the first concise but complete discussion of the significance of the failure of the circulation in its various forms. After a brief introduction in which he gives an interesting historical review of the outstanding contributions to the mechanism of heart failure, followed by a definition of the terms that he is to use in the subsequent chapters, he starts directly with the main discussion. He then takes up what he calls the three main methods by which the circulation fails, the hypokinetic, the hyperkinetic and the dyskinetic syndrome. By hypokinetic circulatory failure is meant an insufficient circulation, such as is found in shock and collapse. The hyperkinetic state signifies an overactive circulation such as occurs in certain nervous conditions, for example, neurocirculatory asthenia and hyperthyroidism. The dyskinetic syndrome indicates the "inefficient" circulation which is present in myocardial weakness or congestive heart failure. Although these terms are rather novel in their application to heart disease, the reader will quickly appreciate their significance and find that they help materially in understanding the nature of heart disease. The last section of the volume considers failure of the coronary circulation (angina pectoris and coronary thrombosis) as a problem that is different from congestive heart failure in many respects.

The outstanding characteristic of this volume is that it puts to physiologic and experimental proof many of the prevailing concepts concerning the nature of heart failure. In one sense it is a summary of an extensive study of this subject that Harrison has been conducting during the past ten years. He draws generously, however, on the work of many other investigators for support of his arguments. Throughout one sees an attempt to explain intelligently phenomena by direct observation of the pathologic physiologic condition of the patient or by experimental work on dogs. In this way light is thrown not only on the major problems in heart disease, such as dyspnea and edema, but on such questions as why the skin of a patient with one type of circulatory abnormality is warm and that of a patient with another type of this disorder is cold.

His main contribution is the discussion of congestive heart failure. He presents convincing evidence to support the proposition that congestive heart failure is not primarily concerned with the lack of output of the heart. It is rather a difficulty or inefficiency of ejecting the volume of blood that the heart puts out, which volume may not be greatly reduced from normal. He supports the theory of "backward failure" (back pressure) rather than that of "forward failure" (diminished output). He believes that dyspnea, edema, congestion and other disorders cannot be due to a diminished flow of blood to the tissues, but rather to a backing up of blood in those vascular areas which drain toward the failing chamber of the heart (in the lungs when the left ventricle fails and in the liver and extremities when the right fails). In this process of failing heart, dilation and increase in pressure proximal to the chamber involved are most important factors. Although an entirely different point of view still prevails in the minds of many of the present American and English authorities on the subject, Harrison's arguments are not new by any means. He merely has accumulated a mass of experimental evidence to support these conceptions.

In addition to the theoretical discussion, this book contains a great deal of practical advice concerning the diagnosis and treatment of heart disease. It therefore can be profitably read by both students and practitioners. In fact, in this



short volume there will be found a great deal of information that is new even to those specializing in cardiovascular disease. It is a most authoritative treatise on this particular subject, and it will repay one manyfold if it is read carefully.

**Spontaneous Pneumothorax in the Apparently Healthy** By Hans Kjaergaard. Paper. Pp 93, with 29 figures and appendix of 51 case histories. Copenhagen: Levin & Munksgaard, 1932.

This dissertation is a detailed study of spontaneous pneumothorax occurring in apparently healthy persons. For this condition Kjaergaard plausibly suggests the term "pneumothorax simplex," which is to be used for all cases of spontaneous pneumothorax occurring without demonstrable cause in healthy persons in whom no sign of tuberculosis can be found and in whom the disease takes an afebrile course without pleural effusion. In this class are also to be included cases in which the patients have a slight rise of temperature in the first week of the illness and cases in which the roentgenograms show the presence of an insignificant pleural exudate, too small to be made out on auscultation.

On the basis of facts obtained on observation of the sixty-one attacks seen in his own series of fifty-one patients and from a study of about two hundred cases reported by other authors, Kjaergaard arrives at important generalizations as to the etiology, pathogenesis, symptomatology, prognosis and therapy. The disease is due to the rupture of a valvular vesicle on the surface of the lung, photographs of such vesicles are given. In one instance the vesicle was seen in a remarkable roentgenogram, which is reproduced opposite page 39. Kjaergaard shows that this disease has nothing to do with active tuberculosis, so that these patients should be spared the loss of time and the expense of treatment in a sanatorium, as well as the fear of pulmonary tuberculosis. In partial pneumothorax the treatment is rest in bed for two weeks. In total pneumothorax, after two weeks of rest in bed cautious aspiration of air may be done. No after-treatment is necessary, and even in chronic pneumothorax that has persisted for more than a year the final outcome often is spontaneous recovery. In persistent cases, however, the intra-pleural injection of 30 cc of a 30 per cent solution of dextrose may be tried. In cases with severe dyspnea it is necessary to quiet the patient with morphine and to do immediate thoracentesis. Suction pumps are not essential in emergencies, one can connect the cannula with a rubber tube and aspirate with a syringe or with one's mouth. If there is hemorrhage, in desperate cases one may consider the possibility of thoracotomy and attempted ligation. In suffocating mediastinal emphysema with pneumothorax the treatment consists in repeated punctures, inhalation of oxygen and stimulation, it may be necessary to make a small median incision in the neck above the sternum and to express the subcutaneous air by stroking.

The book is written in excellent English. A curious feature, which is worth noticing, since it is sure to confuse American readers, is the use of the symbol — to denote subtraction or negativeness, as on pages 30 and 82. While this usage is the rule in Danish, it does not extend to all Scandinavian languages and is unfamiliar even to well read mathematicians. According to Cajor, it is deservedly obsolescent, and one wonders why, in this detail, the University of Copenhagen has not yet joined others in the effort to make mathematics the universal language that it ought to be. In every other respect this book is scholarly and admirable. It is well illustrated, and it deserves to be in the library of every one interested in diseases of the chest.

**Das Extremitäten-, Thorax- und Partial-Elektrokardiogramm des Menschen. Eine vergleichende Studie.** Bands I and II. By F. M. Groedel. Price, 25 marks. Pp 358, with 334 illustrations, 200 plates. Dresden: Theodore Steinkopff, 1934.

This work consists of two volumes, a text and an atlas. The atlas contains two hundred excellent plates of electrocardiographic tracings illustrating the cases and discussions in the text.

The text is divided into two parts. Part I contains a general discussion of the physiology of heart muscle and a brief consideration of the principles of electrocardiography, leading up to a consideration of the partial electrocardiogram. The author considers the conventional electrocardiogram a superimposition of two distinct curves, a dextrogram and a levogram. By the aid of an indifferent electrode and small chest electrodes placed in the region of the lower part of the sternum and the left axilla, curves with constant characteristics are obtained in normal man and experimental animals. These tracings the author terms partial electrocardiograms and puts forth experimental and theoretical evidence to prove that they are dextrograms and levograms. Part II is concerned with the pathologic electrocardiogram. Groedel systematically considers various cardiac abnormalities as they affect the electrocardiogram. Deformities and changes in the partial electrocardiogram are used to localize cardiac damage and demonstrate changes not evident in the usual leads.

Evidence to prove that the partial curves are true dextrograms and levograms does not appear conclusive. Further experimentation on animals would seem most profitable. In the cases reported the electrocardiographic findings appear remarkably clear. However, sufficient postmortem confirmation of the ability of this technic to localize lesions, while most important, is lacking. Such confirmation, whether or not the curves are purely left-sided or right-sided, would establish an important diagnostic procedure and open up a new field in electrocardiography.

The book is of great interest to and should be read by all those engaged in electrocardiography.

**Koronarinfarkt und Koronarinsuffizienz in vergleichender elektrokardiographischer und morphologischer Untersuchung.** By Franz Buchner, Arthur Weber and Berthold Haager. Price, 12 marks. Pp 104, with 131 illustrations. Leipzig: Georg Thieme, 1935.

This work is a comparative electrocardiographic and morphologic study of infarction and insufficiency of the coronary vessels. The text consists of a short discussion of infarction in the various branches, followed by a consideration of insufficiency of the coronary circulation in relationship to aortic syphilis, marked anemia, coronary sclerosis and hypertension. Disseminated necrotic areas resulting from acute coronary insufficiency are described and histories of cases presented, in two cases there were changes in the right ventricle. Electrocardiographic findings resulting from these changes are outlined. Pericarditis and its electrocardiographic changes are also taken up.

The illustrated case reports are excellently arranged, with a photograph of the heart, sectioned to show the gross pathologic picture, a portion of the electrocardiogram, and a diagram of the coronary circulation indicating the pathologic changes present. The important clinical facts are given, with an interpretation of the electrocardiogram, a verbal description of the cardiac pathologic changes and finally an analysis of these findings. The diagrams, photographs and tracings are excellently done and so arranged that those familiar with electrocardiography but with little knowledge of the German language will have no difficulty in understanding the ideas conveyed.

The  $Q_1-T_1$  and  $Q_3-T_3$  types of curves are confirmed as indications of anterior and posterior infarction, respectively. The interpretations given under coronary insufficiency are more often subject to variation. While all will not agree with the authors' correlation of the electrocardiographic findings and the pathologic changes of the coronary vessels, the data are so completely and so clearly given that one may evaluate the findings and interpret them himself. In case eleven, for example, the reviewer was led to different conclusions.

The reviewer can only praise the method of presentation of the data and the thoroughness with which it has been carried out.

**The Principles and Practice of Urology** By Frank Hinman, M D, clinical professor of urology at the University of California Medical School Price, \$10 Pp 1111, with 513 illustrations Philadelphia W B Saunders Company, 1935

The beginning of a recent book notice in *The Journal of the American Medical Association* won this reviewer's heart "This book heralds the return of the larger and more comprehensive textbooks" For some years there has been a lack on our side of the Atlantic, at least, of comprehensive medical textbooks written by a single person whose knowledge of a given subject is broad enough to permeate an entire book, whose literary style is well enough sustained to make whatever he writes of interest and whose enthusiasm is contagious enough to infect an unsensitized reader

Hinman's book is good First, it is well written, so that even a physician can easily perceive something of the charm of urology Second, it is well illustrated, so that matters highly technical to the uneducated mind and eye become fairly clear Third, it has a good index, so that at an instant's notice one can familiarize oneself with anything in the field of urology from the aberrant vas of Haller (a structure which many physicians do not know when they meet it) to the zones of Head

The prefatory *apologia* describes the personality of his book nicely It started, apparently, with the humble object of presenting the principles of urology in practical form to the medical student and the physician in general practice, it ended neither a primer nor a compendium, but a first-class textbook written laboriously and earnestly in an attempt to instruct the medical student, to cover the field of urology for the general practitioner and to serve as a reference book for the complete urologist

Those who dislike the current fashion of many-authored textbooks will welcome this one with eagerness It is a fine achievement

**Biochemistry of Medicine** By A T Cameron and C R Gilmour Second edition Price, \$6 Pp 518, with 31 illustrations Baltimore William Wood & Company, 1935

The appearance of this second edition two years after the publication of the first indicates that the book has been well received by the medical profession This is easily understandable The authors have taken great care in the preparation of the work to make it readable, to make it interesting to the physician in general practice and to reduce to a minimum the chemical features of the text In other words, the book has been prepared with the definite intention of making available for the practitioner of medicine an explanation for the various biochemical reactions that occur in health and disease The results speak for themselves

It is interesting to note that in this second edition it has been necessary largely to rewrite the section on the endocrine glands, and the section on the vitamins might well have been subjected to extensive revision, an interesting observation on the tremendous strides that are being made in the advancement and knowledge concerning these two phases of medicine Particularly to be stressed is the excellent summary at the end of each chapter, which should be read before the main features of that chapter, because in this way the reader gets an excellent general picture in which the details are filled in by the material which is elaborated in the section which precedes the summary Also to be commended is the excellent list of references at the end of each chapter As no attempt has been made, and in fact it would be impossible, to include all references, it might have been of some value to the reader who is not intimately acquainted with biochemistry had the authors been more selective in the use of references and instead of including from 100 to 115, not all of which are outstanding, had utilized one third of the number, as references to the papers that are really worth while and of current importance

**Corazón y vasos** By Dr Pedro Cossio, chief of the section on cardiology of the Argentine Institute for Diagnosis Pp 385, with 266 illustrations and diagrams Buenos Aires "El Ateneo," Libreria científica y literaria, 1935

This book gives an interesting description of the various diagnostic methods now available for the recognition of cardiovascular diseases. The first chapter describes the anatomy and pathologic physiology of the circulatory system. Next is a chapter on the importance of an adequate history, and this lays due emphasis on the proper interpretation of symptoms. Next is an excellent account of how to examine the heart, of the technic of auscultation, percussion and palpation. Much of the remainder of the volume deals with the more mechanical diagnostic methods in general use, the electrocardiogram, the use of the roentgen rays or fluoroscope, sphygmomanometry, arteriography and methods for studying the capillaries. Finally there is a long chapter of fifty-five pages which discusses in detail the interpretation of electrocardiographic tracings.

The charm of the book lies in the manner in which it is written. It is written simply and is well illustrated so that each point which the author wishes to emphasize is clearly set forth. There is no reference to the current literature, the author evidently preferring to have familiarized himself with the ideas of other investigators and then to write from his own point of view. The result is a logical presentation, unusually readable and expressing a sound conception of heart disease. The book has been compiled for the benefit of general practitioners who are interested in modern cardiology. They should appreciate it.

**Die Electrocardiographie und andere graphische Methoden in der Kreislaufdiagnostik** By Prof Dr Arthur Weber, Direktor des Balneologischen Universitäts-Instituts, Bad Nauheim. Second edition. Paper. Price, 15.60 marks, bound, 16.50 marks. Pp 180, with 129 illustrations. Berlin Julius Springer, 1935.

To those interested in graphic methods of studying the circulation this work will furnish a good review of the subject. Weber describes the method of recording heart tones, arteriograms, venous curves, cardiograms and electrocardiograms. All the methods are described in considerable detail. Several varieties of electrocardiograph in use in continental Europe are described. A description of those in common use in America is lacking.

In discussing the different diseases of the circulatory system records are shown and described in which the various tracings are synchronized and superimposed. For example, in the discussion of disease of the mitral valve, a photograph of the heart tones, the venous and arterial curves and the electrocardiogram may be studied all on the same record. The various cardiac arrhythmias are discussed in a similar fashion, as are alternation of the pulse, gallop rhythm and disease of the coronary vessels. Only the conventional three leads of the electrocardiogram are given. No mention is made of leads IV, V and VI that are being discussed in this country at the present time.

There is nothing new in the work, but existing knowledge is well correlated and beautifully set out. An excellent bibliography is a part of the work.

**Traité de gastroscopie et de pathologie endoscopique de l'estomac** By François Moutier. With a preface by Prof P Duval. Price, 120 francs. Pp 347, with 89 figures and 24 plates. Paris Masson & Cie, 1935.

This monograph, an excellent review of gastroscopy, is divided into three parts. The first part contains a dissertation on the history of the instruments and methods, the anatomy of the stomach, instrumentation, orientation and contraindications, the second part deals with the physiologic and morphologic features of the normal stomach as seen gastroscopically, and the third part includes a discussion of the various diseases of the stomach, functional as well as organic.

Moutier presents the material clearly and briefly. He correlates the normal and pathologic, emphasizing a preliminary appreciation of the normal. He appreciates that gastroscopy supplements other methods of clinical study and should be employed when indicated. He shows how the gastroscopic investigations can be correlated with the patient's history and the results of physical examination, roentgen studies and other laboratory studies. Many good roentgenograms and gastroscopic plates are included in the monograph to illustrate findings in various disorders of the stomach.

The treatise is a good collective source of information of the French literature on gastroscopy.

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## News and Comment

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### FIRST INTERNATIONAL CONFERENCE ON FEVER THERAPY

The first international meeting on fever therapy will be held in New York in September 1936. The conference will aim to collect and crystallize available data regarding the use of fever induced by physical and other agencies as a therapeutic procedure. Therapeutic, physiologic and pathologic phases of fever will be discussed. Those interested in participating are requested to make early application to the secretary, Dr. William Bierman, 471 Park Avenue, New York. It is planned to translate abstracts of all the papers into French, English and German. Manuscripts and abstracts should be in Dr. Bierman's hand not later than June 1, so that printed copies of the translations may be available for the conference.

# Archives of Internal Medicine

VOLUME 57

APRIL 1936

NUMBER 4

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## A STUDY OF THE LOWER LOBE OF THE LUNG

AN EXPLANATION OF ROENTGENOLOGIC SHADOWS

JOSEPH LEVITIN, M D

AND

HAROLD BRUNN, M D

SAN FRANCISCO

The interpretation of roentgenograms is dependent on two essential factors (1) knowledge of the anatomy of the part examined, and (2) an interpretation of the disease process in terms of variations in density noted on the roentgenogram. Any addition to the knowledge of roentgenologic anatomy would aid in the interpretation and localization of shadows seen on the roentgenogram. This paper is presented as a contribution to the roentgenologic knowledge of the anatomic structure of the lower lobes of the lungs.

Anatomically, the right lung is divided into three lobes, the upper, the middle and the lower, by two interlobar fissures, and the left lung is divided into two lobes, the upper and the lower, by one interlobar fissure. The course of the major fissures on both sides is from the level of the spinous process of the third dorsal vertebra posteriorly, obliquely downward and forward to the costochondral articulation of the sixth rib anteriorly. On the right side another fissure extends horizontally forward from the axilla to the costochondral articulation of the fourth rib. It separates the superior lobe above and the inferior lobe below.

Our studies indicate that the lower lobe on each side is divided into two parts. The division can be proved anatomically, embryologically and by a study of the bronchial distribution to the lower lobe. At times, a fourth lobe on the right side and a third lobe on the left side may be present as an anomaly when fusion between the two divisions of the lower lobe has failed to take place. Each of the two divisions may be, and often is, separately involved by a disease process and each gives different shadows on the roentgenogram. We have called the upper part of the lower lobe the superior division and the lower portion the inferior division. In the lateral view the superior division is well

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This work was assisted by a grant from the Lily Spreckels Weggeforth Fund From the Department of Roentgenology, Mount Zion Hospital, and the University of California Thoracic Clinic

seen on the roentgenogram as a triangular area posteriorly placed, with the apex at the hilus. The upper border of this division corresponds to the interlobar septum between the upper and the lower lobe. The lower border corresponds to an imaginary line drawn from the hilus backward and downward to the eighth rib posteriorly. The second, or inferior, division of the lower lobe is the major division and takes up the remaining portion of the area occupied by the lobe (fig 1).

A study of the bronchi distributed to the lower lobe again marks out the division of the superior and inferior portion of the lower lobe. Two distinct bronchial distributions are always present to the two divisions of the lobe. This fact was established by a study of roentgenograms of postmortem specimens, with the bronchi of the lower lobe filled with 30 per cent bismuth subnitrate in petrolatum.

The first branch from the main bronchus to the lower lobe of the right lung rises opposite the bronchus of the middle lobe. This branch

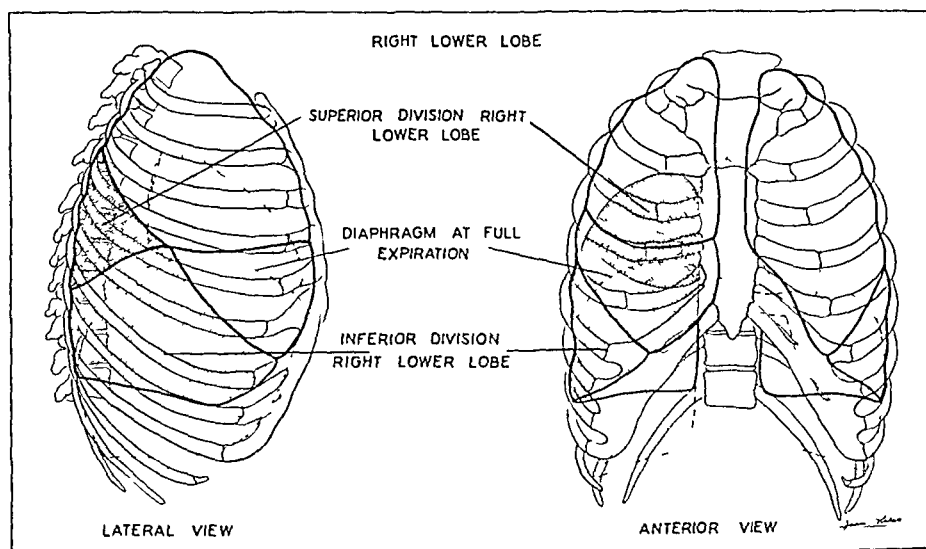


Fig 1—Diagram of the lower lobe of the right lung. The lower lobe of the left lung has a similar superior and inferior division, for the sake of brevity and clarity it has been omitted.

is directed posteriorly and soon divides into smaller branches, all of which are distributed only in the superior division. In the left lung the first branch rises from the main bronchus at the same level, in a comparable position, and is likewise directed posteriorly. The main stem of the bronchus to the lower lobe continues downward for about 1 cm and then divides into three secondary bronchi in the right lung and two secondary bronchi in the left lung. These bronchi are distributed only to the inferior division (fig 2). There is no overlapping of bronchial distribution between the superior and the inferior division. They are as distinct from one another as the bronchi to the upper lobe are distinct from the bronchi to the middle lobe.

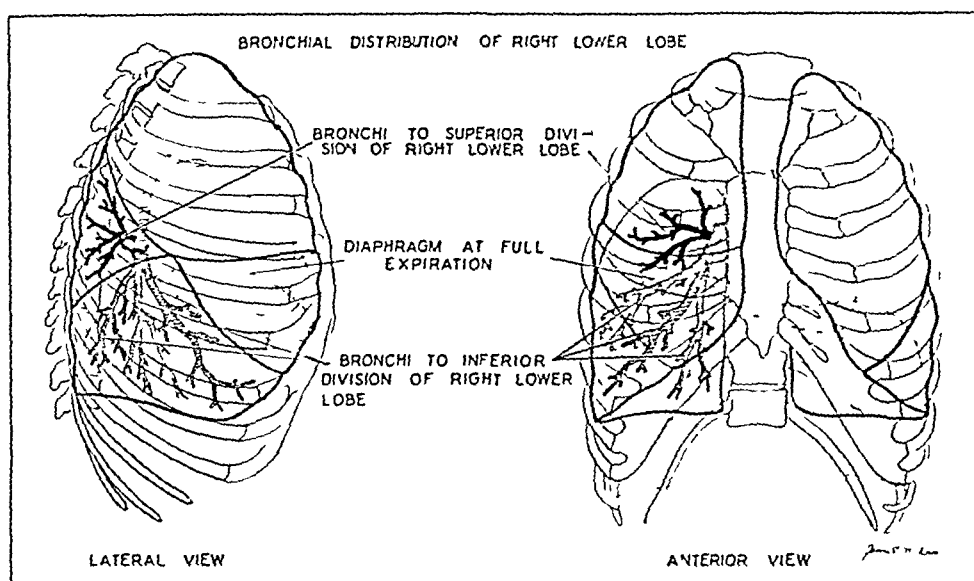


Fig 2—Diagram of the bronchial distribution of the lower lobe of the right lung. The lower lobe of the left lung has a similar division of the bronchi, for the sake of brevity it has been omitted.

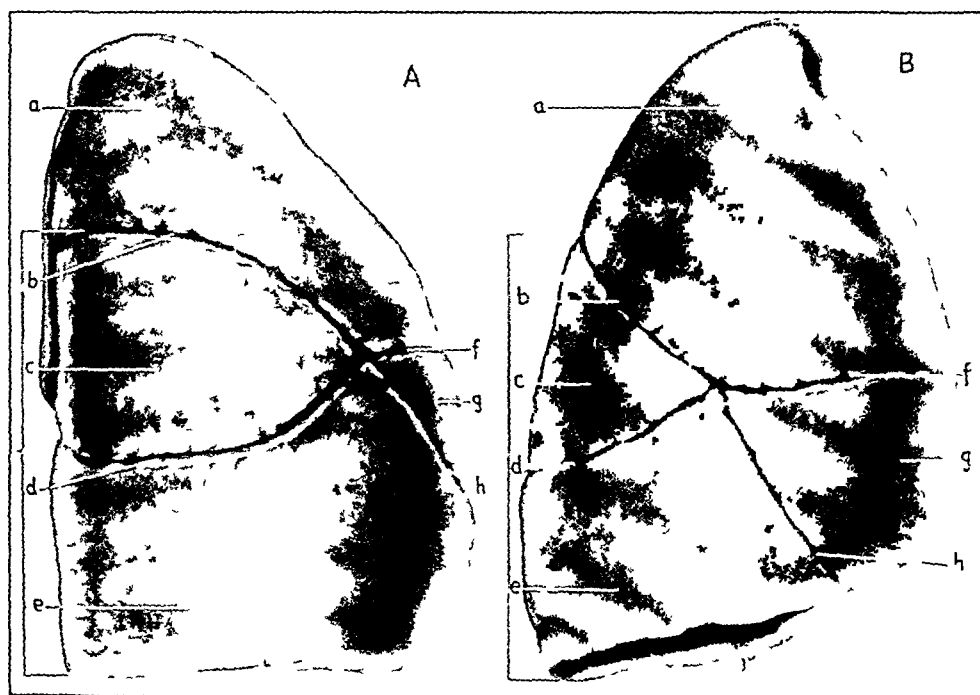


Fig 3—A is a diagrammatic drawing of the posterior view of a four-lobed right lung. B is a diagrammatic drawing of the lateral view. In both drawings a indicates the upper lobe, b, the fissure between the upper and the lower lobe, c, the superior division of the lower lobe, d the fissure dividing the lower lobe into two parts, e, the inferior division of the lower lobe, f, the fissure between the upper and the middle lobe, g the middle lobe and h the fissure between the middle and the lower lobe. The bracket indicates the lower lobe.



An intralobar fissure may be observed completely dividing the two parts, similar to the interlobar fissure dividing the main lobes, as described previously. The division of the lower lobe by a fissure may be partial or complete. Figure 3 depicts a right lung removed at autopsy, showing the lower lobe divided into a superior and an inferior division by a complete fissure. Fusion had failed to take place. It is not uncommon to note a shallow fissure or a sharp dimpling in a normal specimen, marking the limit of fusion of the superior to the inferior part of the lower lobe (fig 3 *A* and *B*).

It is interesting to know that this division of the lobe has an embryonic origin which determines its distinct bronchial distribution. In a review of the embryonic development of the bronchi (Keibel and

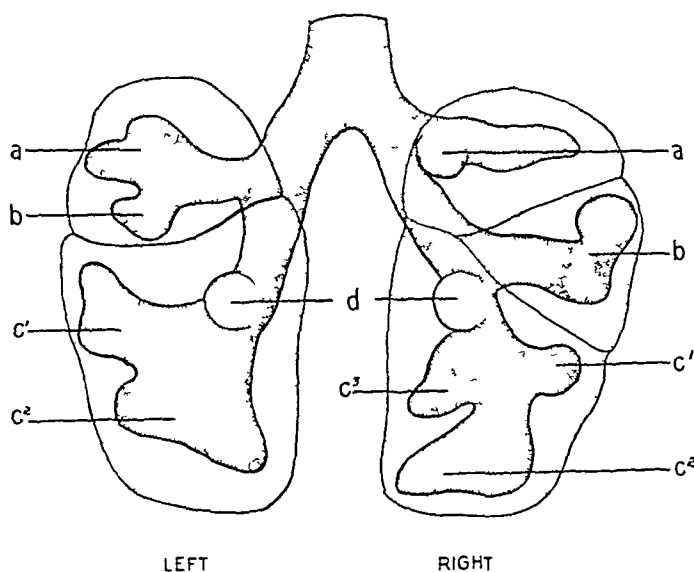


Fig 4—An embryo at the beginning of the fifth week, viewed from behind. In this illustration *a* indicates the bronchus to the upper lobe, *b*, the bronchus to the middle lobe on the right side and to the upper lobe on the left side, *c*<sup>1</sup> and *c*<sup>2</sup>, bronchi to the inferior division of the lower lobe, *c*<sup>3</sup>, the infracardial bronchus on the right side to the lower lobe, and *d*, the bronchus to the superior division of the lower lobe. (From Keibel and Mall,<sup>1</sup> after Merkel, 1902.)

Mall<sup>1</sup>) one notes that the bronchus to the superior division of the lower lobe develops from an anlage which is distinct from the anlage of the bronchi to the inferior division of the lower lobe. In an embryo of 11 mm the anlage for the main bronchi is well established (fig 4). On the right side is the anlage of the apical bronchus (*a*), extending dorsolaterally, which is to supply the upper lobe of the right lung. The anlage for the lateral first ventral bronchus (*b*) is present to supply

1 Keibel, F, and Mall, F P. Manual of Human Embryology, Philadelphia, J B Lippincott Company, 1912, vol 2, p 482.

the middle lobe. The left side differs in that the anlage *a* and *b* have a common stem to supply the single upper lobe. Next in order is the anlage *d*, which arises separately and develops into the bronchus for the superior division of the lower lobe. The main stem continues downward and ventrally and gives rise to two main bronchial anlagen on the left (*c*<sup>1</sup> and *c*<sup>2</sup>) and three on the right. The additional bronchial anlage on the right side is for the infracardial bronchus (*c*<sup>3</sup>).

A 13 mm embryo shows the anlage for the lobes well established and explains the formation of the fissures (fig 5). On the right side are a bud for the upper lobe (*A*) and one for the middle lobe (*B*). There is a small, shallow furrow between them which will form the interlobar fissure. On the left side one large bud contains the bronchi

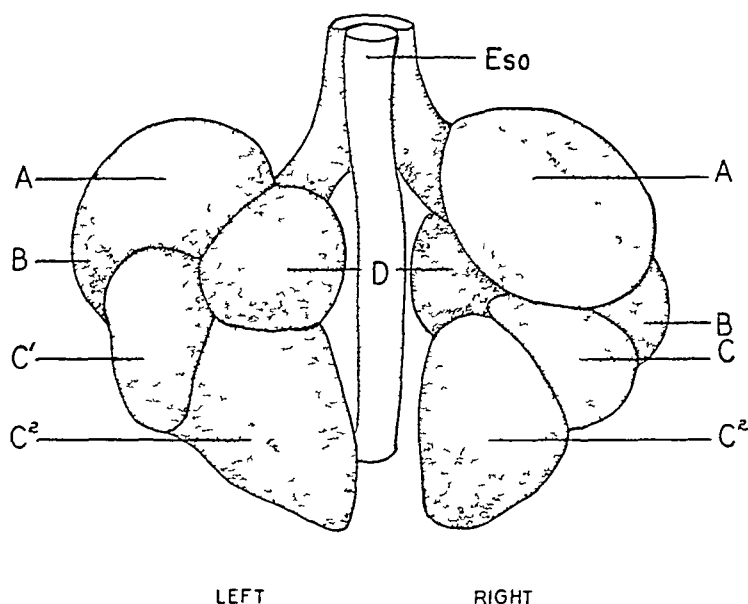


Fig 5—Lung anlage of an embryo of about 13 mm, viewed from behind. *A* indicates the lung bud for the upper lobe, *B*, the lung bud for the middle lobe on the right side (note how on the left side the comparable bud is joined with *A* to form a large upper lobe), *C*<sup>1</sup> and *C*<sup>2</sup>, lung buds for the inferior division of the lower lobe, and *D*, the lung bud for the superior division of the lower lobe (From Keibel and Mall,<sup>1</sup> after Blisnianskaja, 1904.)

(*A* and *B*) for the single upper lobe of the left lung. Three buds are present for the lower lobe (*C*<sup>1</sup>, *C*<sup>2</sup> and *D*). Of particular note is the bud for the dorsal bronchus (*D*). This is definitely separated by a furrow from the other buds. If the furrow persists, a fissure will be present separating this part of the lobe, resulting in four distinct lobes on the right and three distinct lobes on the left side (fig 3). If a complete fusion of all the lung buds of the lower lobe takes place, the result will be a single lower lobe. This follows the anatomic description as previously given and as described in textbooks of

anatomy If fusion of the buds is incomplete, a fissure will remain, with a reflection of pleura, producing an intralobar fissure On the roentgenogram the fissure can sometimes be seen as a pleural line extending from the parietal pleura into the parenchyma of the lung This shadow has often been misinterpreted as a pleural adhesion The fissure may extend all the way to the hilus completely dividing the lower lobe into two distinct lobes (fig 3)

Other writers have recognized two divisions of the lower lobe, either anatomically or as affected by a disease process, without recognizing the anatomic basis or the embryologic origin for this division

Pohl<sup>2</sup> described the apical region of the lower lobe as sometimes set off so as to become an independent lobe He stated that it is noted frequently at autopsy and is recognizable roentgenologically only in a pathologic state

Kramer and Glass<sup>3</sup> studied the roentgenologic localization of abscess of the lung and divided the lung into segments corresponding to the main bronchial divisions They set off an apical posterior triangular area, which they called the apical middle paravertebral segment This is similar to the superior division already described

The superior division of the lower lobe is the one most frequently involved in pneumonic processes At present we can offer no explanation for this The bronchi to this part of the lobe are the only ones that are directed posteriorly, so that with the patient in the prone position they are the most dependent bronchi The action of gravity on secretions in these bronchi may be of some significance The appearance on the roentgenogram of a disease process in this part of the lobe depends on the position of the diaphragm If the chest is well expanded and the diaphragm is low the disease process appears relatively high in the chest Shadows of this sort often have been interpreted roentgenologically as evidence of central pneumonia The physical signs of the process are all posterior, in a small area between the vertebral border of the scapula and the vertebral column and from the fourth to the eighth ribs

#### OBSERVATIONS ON CASES

The roentgenograms for case 1 are illustrative of the appearance of a pneumonic process in the superior part of the lobe when the diaphragm is at full inspiration

CASE 1 (fig 6)—In J W, a man aged 63, on the third day following an operation for a ventral hernia cough developed, and the temperature rose to

2 Pohl, R Der Lobus Posterior der Lunge, Fortschr a d Geb d Rontgenstrahlen **46** 583 (Nov) 1932

3 Kramer, B, and Glass, A Bronchoscopic Localization of Lung Abscess, Ann Otol, Rhin & Laryng **41** 1210, 1932

38 C (100.4 F) Physical signs were not present at first, but the next day an area of dulness with impaired breath sounds was noted on the right side posteriorly. A roentgenogram showed an area of increased density extending from the hilus in the middle of the pulmonary field. The condition was diagnosed central pneumonia. The lateral view showed the process to lie posteriorly, to be triangular and to conform closely to the area designated as the sup-

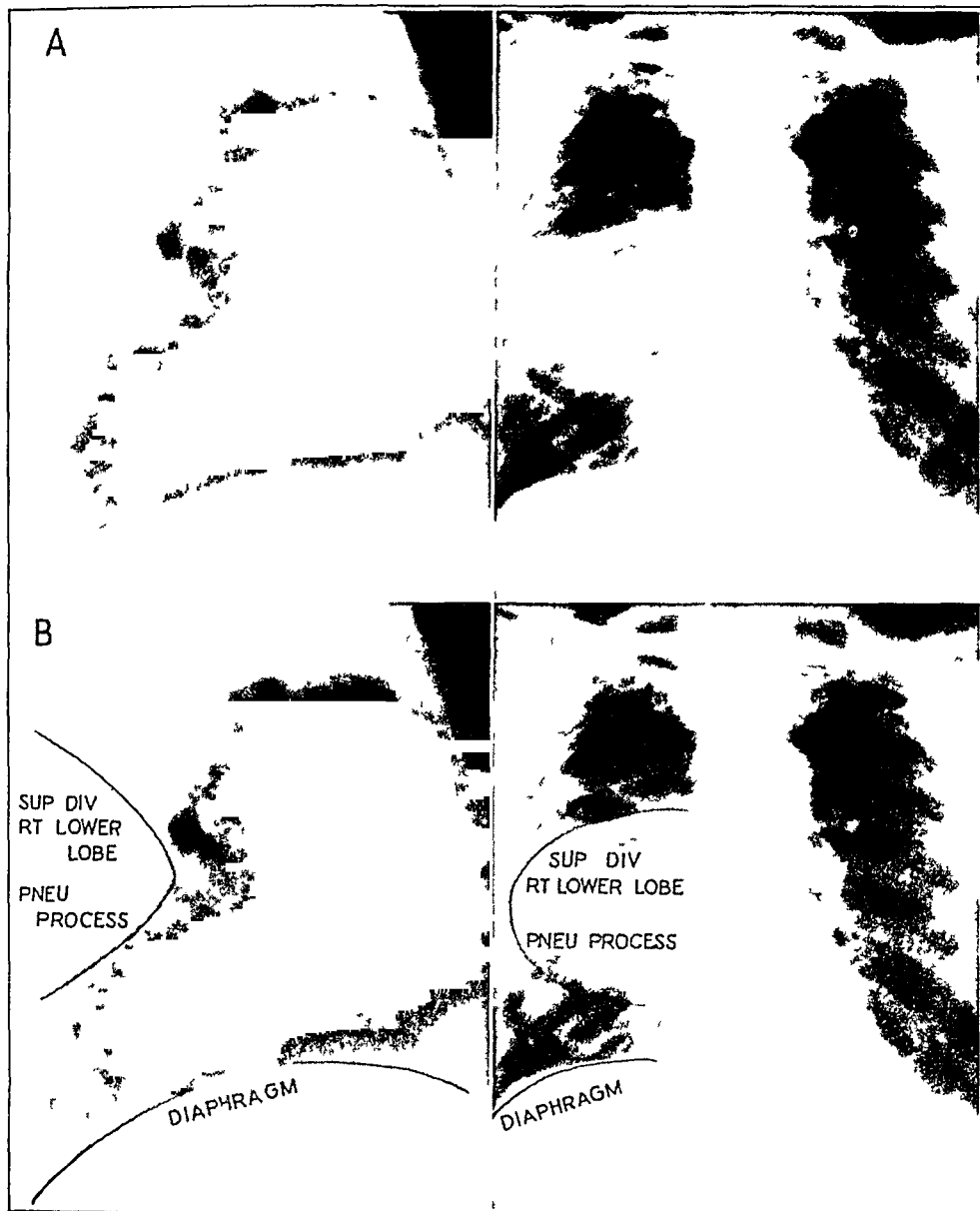


Fig 6—A pneumonic process involving the superior division of the lower lobe of the right lung. The diaphragm is at full inspiration. This is often called central pneumonia.

rior division of the lower lobe. The process in the lobe developed into an abscess of the lung, and the patient subsequently died. Autopsy confirmed anatomically the location of the process.

The roentgenograms for case 2 illustrate the appearance of the process when the diaphragm is in midway position.

CASE 2 (fig 7)—J C, a man aged 37, had a history of an inflammatory process, following an operation, which developed into a chronic abscess of the lung. The diaphragm on the right side was considerably higher than that on the left, and in the postero-anterior view the area of involvement appeared to occupy the lower half of the chest. The lateral view clearly demonstrated the posterior location of the process, which was triangular and conformed closely to the outline of the superior division of the lower lobe.

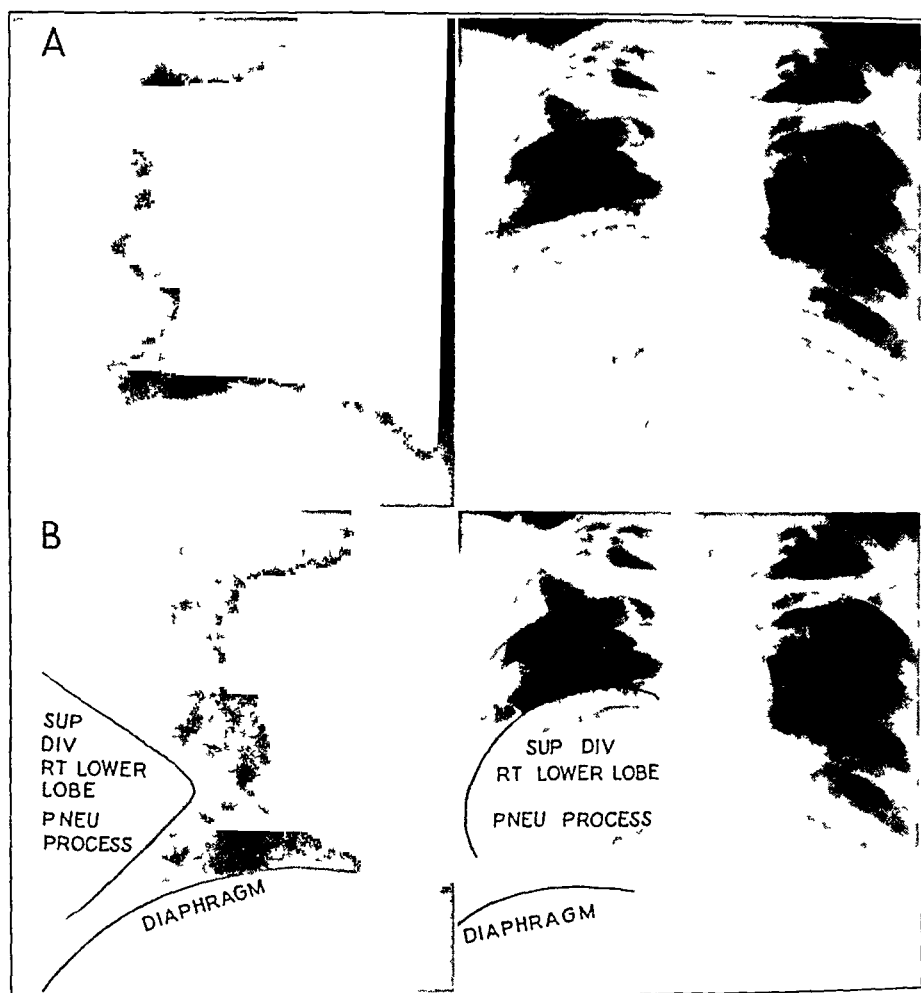


Fig 7—A pneumonic process involving the superior division of the lower lobe of the right lung. The diaphragm is in a midway position.

The roentgenograms for case 3 also illustrate the appearance of a pneumonic process in the superior division of the lower lobe when the diaphragm is partially elevated.

CASE 3 (fig 8, courtesy of Dr E. Wolff)—E M, a boy aged 7 years, had a sudden onset of fever, with pain in the right side of the chest and rapid respiration. Physical examination showed an area of dullness in the right side of the chest posteriorly, with diminished breath sounds. The diagnosis was pneumonia of the lower lobe of the right lung. The roentgenogram of the postero-anterior

view showed an area of increased density occupying the lower half of the right side of the chest. The lateral view showed the process to lie posteriorly in the region of the superior division of the lower lobe.

When the diaphragm is at the full extent of expiration the highest point lies on a level with the fourth rib anteriorly. If the superior division of the lower lobe is involved by a pneumonic process this part

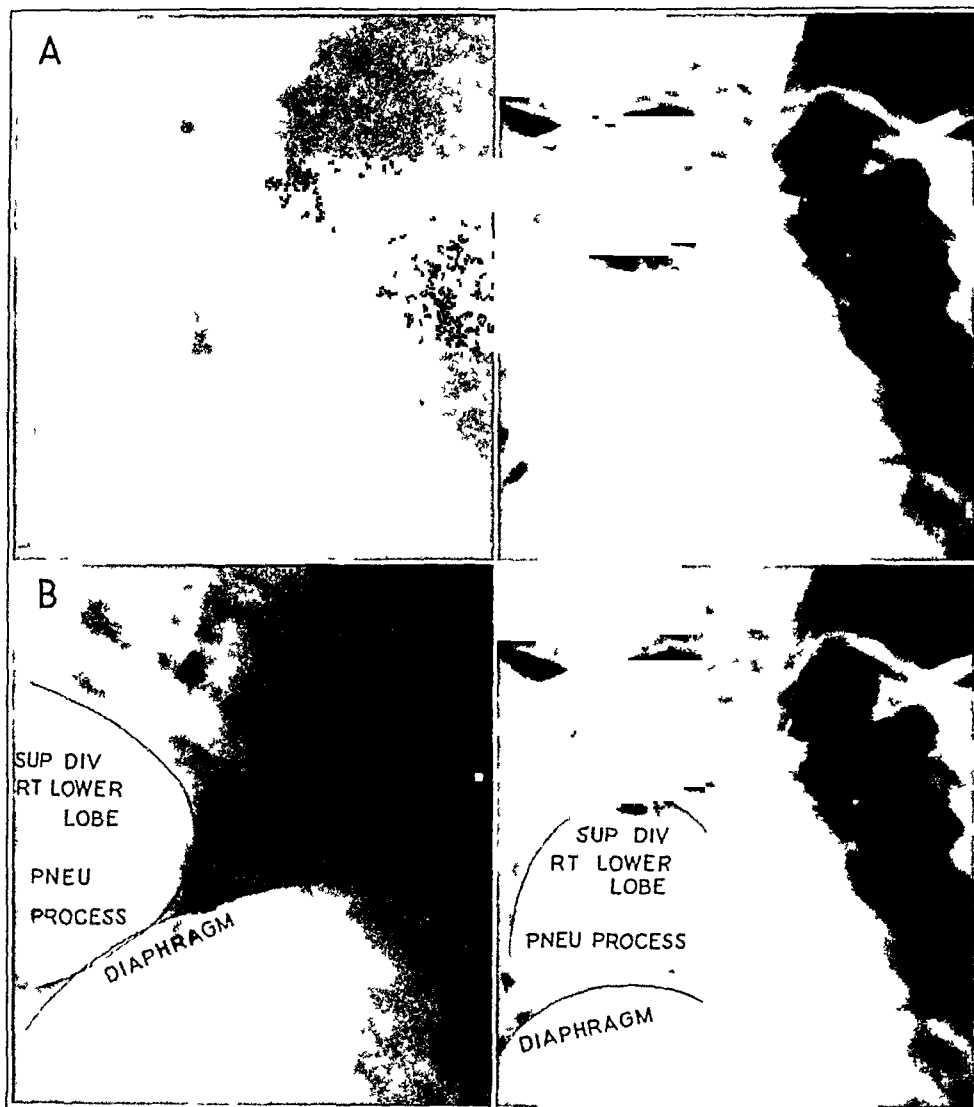


Fig 8—A pneumonic process in the superior division of the lower lobe of the right lung. The diaphragm is partially elevated.

of the involved lung appears to lie in the recess behind the diaphragm. It may be mistaken for encapsulated fluid.

The roentgenograms for case 4 illustrate a pneumonic process in the superior part of the lobe and its appearance with the diaphragm at full expiration.

CASE 4 (fig 9, courtesy of Dr A L Brown)—H D, a girl aged  $4\frac{1}{2}$  years, had a sudden onset of abdominal pain in the right lower quadrant, which gradually spread through the whole abdomen. The temperature was 102 F. A diagnosis of acute appendicitis was made. At operation pneumococccic peritonitis was noted. The temperature postoperatively continued to be about 40 C (104 F), the pulse rate was from 130 to 140, and the respiratory rate was from 30 to 40. Three weeks following the operation a roentgenogram of the chest showed grayness at the base of the right lung, well seen in the lateral view as a dense, well

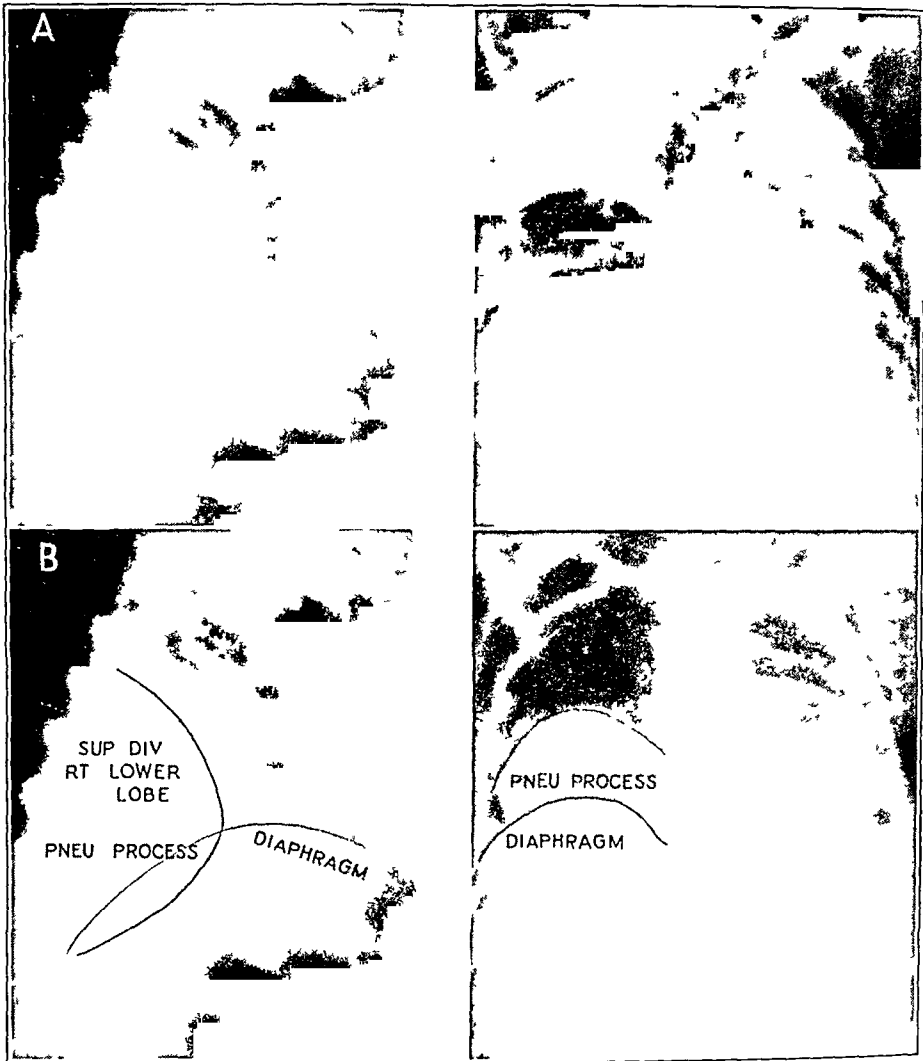


Fig 9—A pneumonic process in the superior division of the lower lobe of the right lung. The diaphragm is elevated. The disease process appears to lie in the recess behind the diaphragm. It was misinterpreted as encapsulated fluid.

demarcated shadow lying in the posterior recess behind the diaphragm. Interpretation of the roentgenogram was encapsulated fluid. Repeated attempts at aspiration failed to obtain fluid. Further study of the shadow, its location and shape, showed its close similarity to the area occupied by the superior division of the lower lobe. The diagnosis was then changed to that of pneumonic consolidation of this part of the lobe. The further clinical course confirmed the diagnosis.

The inferior division of the lower lobe while not as frequently involved by disease processes, also has its characteristic shadow. Most of the involved area of the lung is masked by the shadow of the liver. In the postero-anterior view, an area of increased density is shown



Fig 10—A pneumonic process involving the inferior division of the lower lobe of the right lung

lying above and continuous with the shadow of the liver. In the lateral view most of the process is also masked by the shadow of the liver. An area of increased density occupies the part of the lung in the recess behind the diaphragm. This part of the lobe is frequently



involved by postoperative atelectasis. One may account for this fact by the action of gravity on the secretions in the bronchi when the patient is in the upright or semirecumbent position.

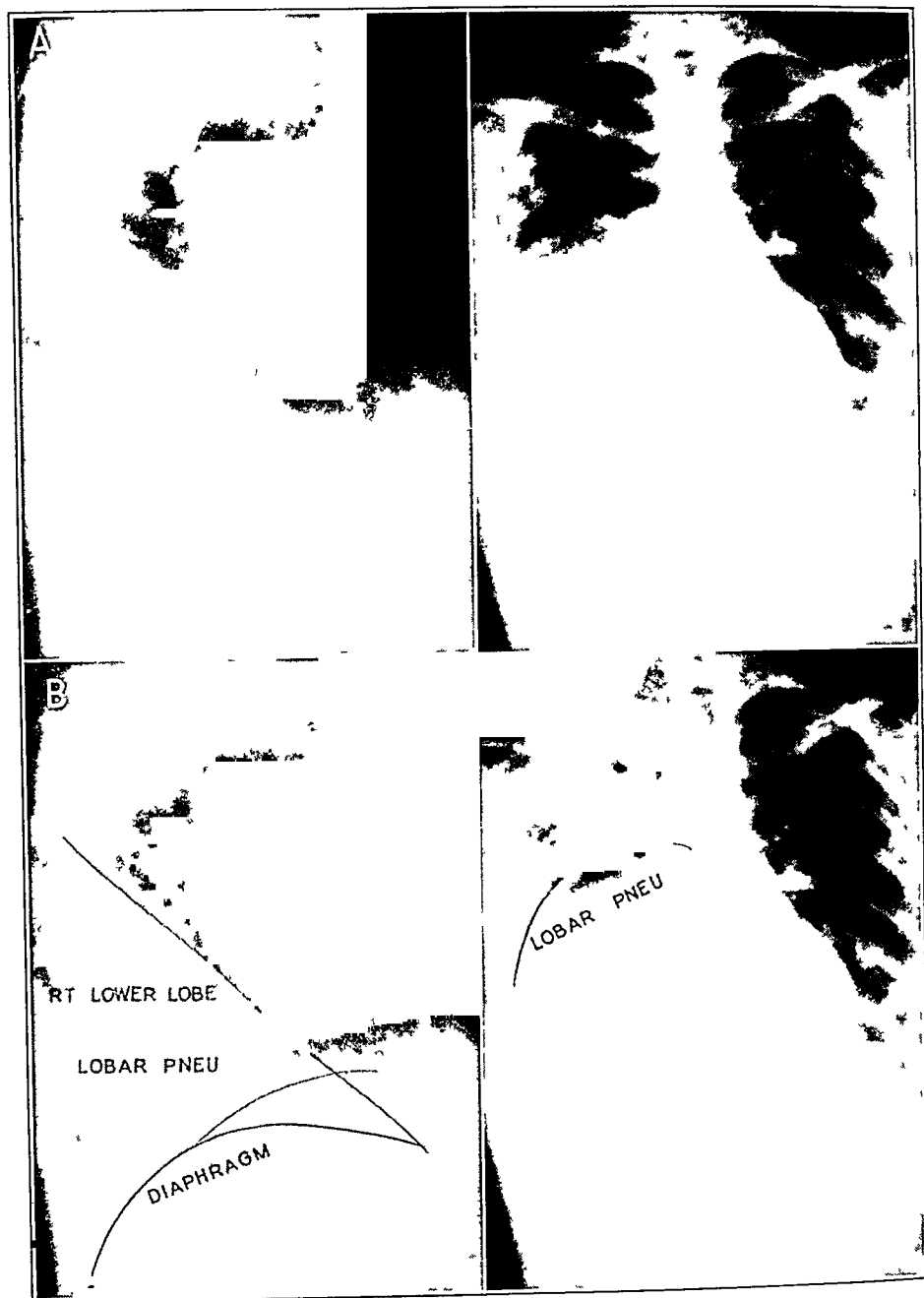


Fig 11—Lobar pneumonia involving the entire lower lobe (superior and inferior divisions) of the right lung

The roentgenograms for case 5 (fig 10), observed through the courtesy of Dr L C Jacobs, illustrate the pneumonic process of the inferior division of the lower lobe

The whole lobe, i e, the superior and inferior divisions, may be involved by a pneumonic process. The shadow on the roentgenograms for case 6 is a combination of the shadows of involvement of the superior and the inferior division of the lower lobe.

CASE 6 (fig 11, courtesy of Dr F Firestone) —P H, a woman aged 25, had a sudden onset of chill, pain in the chest and cough. The temperature was 40 C (104 F), the pulse rate 120 and the respiratory rate 39. Physical examina-



Fig 12—A pneumonic process involving the superior division of the lower lobe of the left lung.

tion revealed dullness of the lower lobe of the right lung, with bronchophony and tubular breathing. Roentgenograms showed an area of density involving the entire lower lobe. The diagnosis was lobar pneumonia. This was confirmed at autopsy.

The lower lobe of the left lung is as frequently involved by a disease process as the lower lobe of the right lung. The appearance on the roentgenogram is similar to that on the right side.

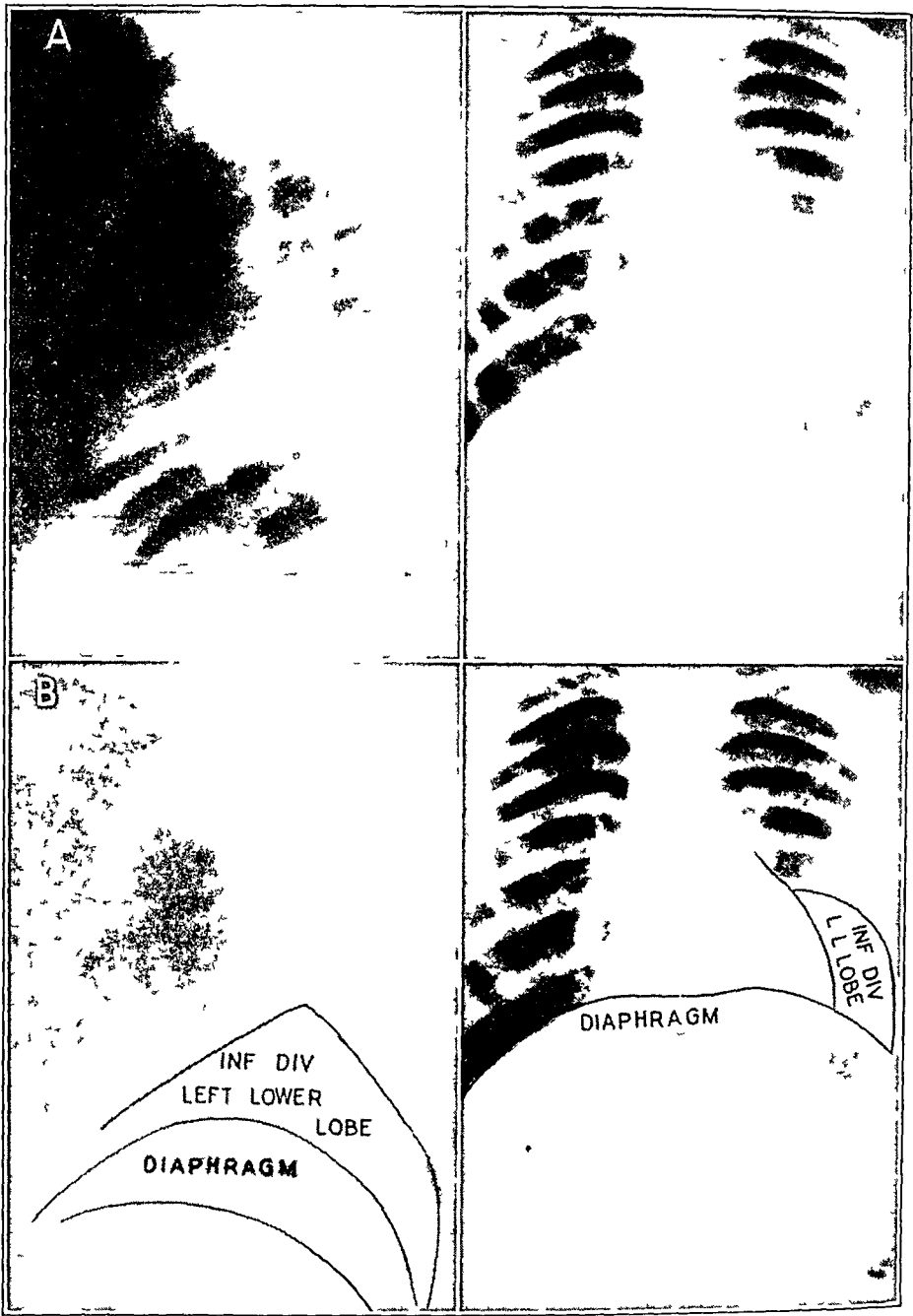


Fig 13—Atelectasis of the inferior division of the lower lobe of the left lung. The involved lung has a tented appearance. The diaphragm is elevated and extends to the superior division of the lower lobe. This aerated lung of the superior division may mask the physical signs of a collapsed lung.

The roentgenograms of the following cases illustrate disease processes in the lower lobe of the left lung

CASE 7 (fig 12, courtesy of Dr G J Heppner)—A S, a girl aged 7 years, had an onset of pain in the chest, with cough. The temperature was 105 F, the pulse rate 130, and the respiratory rate, 30. Physical examination revealed an area

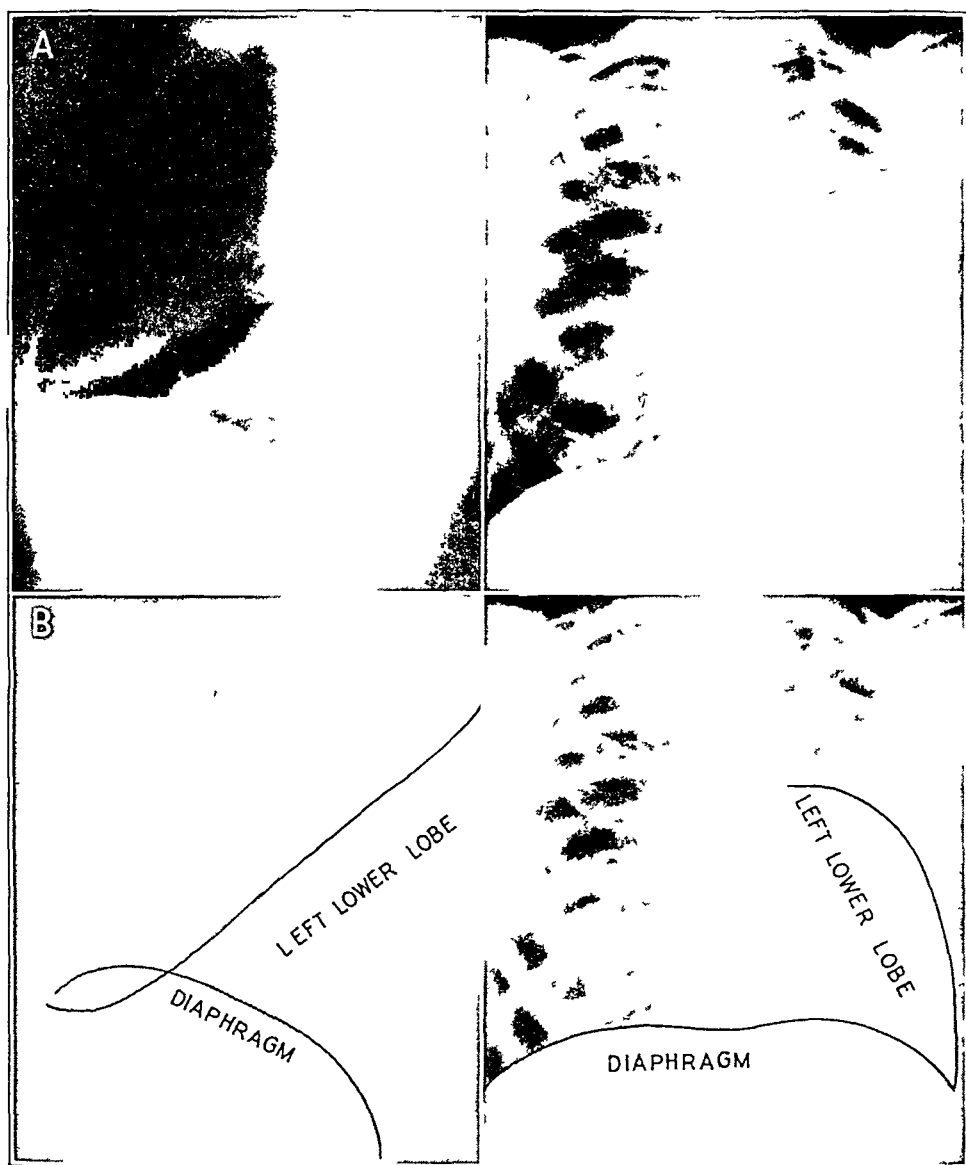


Fig 14—Atelectasis of the entire lower lobe (superior and inferior divisions) of the left lung

of dulness on the left side posteriorly between the scapula and the spine. There were increased breath sounds and bronchial breathing. The diagnosis was pneumonia and was confirmed by the roentgenogram. The patient recovered. The process cleared in five days.

The roentgenograms for case 8 illustrate atelectasis of the inferior division of the lower lobe of the left lung.

CASE 8 (fig 13, courtesy of Dr E Wolff) —C G, a boy aged 10 years, had an infection of the upper respiratory tract followed three weeks later by a non-productive cough and a slight elevation of temperature to 99 F. Physical examination revealed dulness of the base of the left lung posteriorly, with absence of breath sounds. The diagnosis was atelectasis of the inferior division of the lower lobe of the left lung resulting from a plug of the bronchus by mucous secretions. The patient recovered, and the process in the lung cleared.

Case 9 illustrates atelectasis of the entire lower lobe of the left lung.

CASE 9 (fig 14, courtesy of Dr L H Briggs) —J O, a man aged 47, suffered from loss of weight and cough. Physical examination revealed emaciation and an area of dulness involving the left side of the chest posteriorly and in the axilla. A roentgenogram showed complete atelectasis of the lower lobe of the left lung. Bronchoscopic examination revealed bronchial carcinoma occluding the primary bronchus to the lower lobe of the left lung.

#### SUMMARY

The lower lobes of the right and left lungs are divided into two distinct parts: (1) a small triangular superior division and (2) a larger inferior division. This anatomic fact has been insufficiently emphasized in the past. Each portion of the lobe has its own bronchial distribution. Embryologically, each develops from a separate anlage. A fissure separating the two parts may be observed in the developed lung. The pleural reflection in the fissure may be noted in the roentgenogram and has often been misinterpreted as a pleural adhesion. This definite anatomic structure accounts for numerous limited disease processes the localization of which has previously not been understood.

In the roentgenogram the involved superior division appears to lie high in the chest or low behind the diaphragm, depending on the position of the diaphragm when the film is made. Failure to recognize the importance of the position of the diaphragm has often led to misinterpretations.

When the process appears high in the roentgenogram, it is often diagnosed as central pneumonia. When the process appears low on the roentgenogram, it may be mistaken for encapsulated fluid.

NOTE—Since this article was submitted for publication, two other writers have noted a division of the lower lobe as involved by a disease process. Jonsson<sup>4</sup> demonstrated a separate bronchial division to these two parts and observed that silicotic changes occur most abundantly in the inferior part of the upper lobe and the superior part of the lower lobe, the inferior part of the lower lobe was not involved by silicosis.

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4 Jonsson, C. Some Roentgenological Observations Regarding Pulmonary Silicosis in Porcelain Workers, *Acta Radiol* 16 431, 1935.

Westermarck<sup>5</sup> also demonstrated the two distinct bronchial divisions of these two portions of the lower lobe and demonstrated atelectasis as it occurred with tuberculosis as affecting either the superior or the inferior part of the lower lobe. Neither of the aforementioned writers demonstrated an anatomic or embryologic basis for this division.

Mr J Kelso, medical artist and photographer, made the reproductions of roentgenograms and the drawings

516 Sutter Street

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5 Westermarck, N. Entwicklung und Vorkommen von Atelektase bei Lungentuberkulose, *Acta Radiol* **16** 531, 1935

# FACTORS RESPONSIBLE FOR JAUNDICE IN SYPHILIS

WITH SPECIAL REFERENCE TO THE RÔLE OF THE ARSPHENAMINES

ROBERT V SAGER, M D

NEW YORK

For at least four hundred years physicians have known of the occurrence of jaundice with syphilis (Paracelsus,<sup>1</sup> 1510) The introduction of arsphenamine seems to have increased the incidence and the complexity of this condition Since in syphilis, as in any other disease, treatment is necessarily guided by the concepts of etiology, it is of paramount importance to determine the exact causes of the jaundice To this end in the present study I proposed to investigate the factors concerned in the occurrence of jaundice with syphilis and to correlate them with recent acquisitions to the clinical, experimental and pathologic knowledge of disease of the liver

In the discussion of this subject it is necessary at the outset to define certain terms and concepts that are employed The term the arsphenamines is used to indicate the entire family of organic arsenical antisyphilitic preparations, all of which are associated with the condition herein discussed It is clear from clinical experience and from the work of Luethlen<sup>2</sup> and others that the toxic actions of the arsphenamines, on the one hand, and those of its constituent parts per se—arsenic and benzene—on the other, are different This is true quantitatively even more than qualitatively The hepatotoxic power of the arsphenamines is incomparably greater than that of inorganic arsenic

Benign nonobstructive jaundice and acute yellow atrophy occurring in untreated persons with syphilis in the secondary stage are called *icterus syphiliticus praecox* The same complications of secondary and tertiary syphilis occurring while the patient is under treatment with the arsphenamines are called early icterus, if the jaundice appears within ten months after the cessation of treatment, it is called late icterus Under the term paratherapeutic icterus are included both early and late

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From the Medical Service of Dr B S Oppenheimer, The Mount Sinai Hospital

This study was aided by a grant made to the Emanuel Libman Fellowship Fund in memory of Theresa Backer

1 Paracelsus, cited by Proksch, J K Paracelsus *uber die venerischen Krankheiten und die Hydrargyrose*, Med-Chir Centralbl **17** 289, 313, 337, 361, 387, 411, 434 and 458, 1882

2 Luethlen, F Die experimentelle Analyse der Salvarsanwirkung, Ztschr f Exper Path u Therap **13** 493, 1913

icterus Benign jaundice designates the condition in patients who make a complete recovery Acute yellow atrophy is used for convenience to designate the condition in all fatal cases of jaundice in which it is proved pathologically to be acute, subacute or even chronic yellow atrophy, the last of which is more properly termed coarse nodular or toxic cirrhosis It is obvious that in a case of jaundice with syphilis the diagnosis of paratherapeutic icterus cannot be made until all other types of jaundice are excluded, for instance, all hemolytic and obstructive types

General confusion is fostered by an inadequate classification of the subject Some authorities, for instance, have held that the cause of acute yellow atrophy following treatment with arsphenamine differs from that of benign paratherapeutic icterus (Kerl,<sup>3</sup> Herxheimer<sup>4</sup>), others have contended that early and late icterus are essentially different (Pulvermacher,<sup>5</sup> Wosegien<sup>6</sup>) and many have made complicated differentiations on decidedly questionable grounds

Clinically, benign paratherapeutic jaundice simulates so-called catarrhal jaundice, which since the earliest observations (Chauffard,<sup>7</sup> Heitler<sup>8</sup>) has been recognized more and more clearly as a parenchymatous degenerative process in the liver Since the number of fatal cases is usually far smaller than the number of cases of the benign variety, one may conclude that in the cases of the benign type the condition is acute or subacute yellow atrophy *en miniature* and differs from acute yellow atrophy only in severity Indeed, Eppinger,<sup>9</sup> Klemperer, Killian and Heyd,<sup>10</sup> Wallgreen,<sup>11</sup> Huber and Kausch,<sup>12</sup> and Albot<sup>13</sup> were fortunately

3 Kerl, W Schädigungen durch Salvarsan, in Jadassohn, J Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol 18

4 Herxheimer, G Ueber akute gelbe Leberatrophie, Syphilis und Salvarsan, Berl klin Wchnschr **57** 369 (April 19) 1920

5 Pulvermacher, L Zur Frage des Spatikterus nach Salvarsan, Dermat Ztschr **27** 199, 1919, **24** 577 and 648, 1917

6 Wosegien, H Ueber Ikterus nach Salvarsanbehandlung des Ikterus, Arch f Dermat u Syph **1** 139, 1920

7 Chauffard, A Contribution a l'etude de l'ictère catarrhal, Rev de med **5** 9, 1885

8 Heitler, M Ueber Ikterus typhoïdes, Wien Med Wchnschr **37** 958, 1887

9 Eppinger, H Spezielle Pathologie des Ikterus, in Kraus, F, and Brugsch, T Spezielle Pathologie und Therapie innerer Krankheiten, Vienna, Urban & Schwarzenberg, 1923, vol 6, Verhandl d deutsch path Gesellsch **18** 272, 1921, Ueber Ikterus, Klin Wchnschr **1** 1182, 1922

10 Klemperer, P Killian, J A, and Heyd, C G The Pathology of Catarrhal Icterus, Arch Path **2** 631 (Nov) 1926

11 Wallgreen, A An Epidemic of Catarrhal Jaundice, Acta med Scandinav (supp) **26** 118, 1928

12 Huber, O, and Kausch, W Zur Klinik der subakuten Leberatrophie, Berl klin Wchnschr **57** 81, 1920

13 Albot, G Hepatites et cirrhoses, Paris, Masson & Cie, 1931



able to verify this observation in patients with catarrhal jaundice who had died by accident or who had had material from the liver subjected to biopsy. I have recently observed on postmortem examination the same condition in the liver of a patient recovering from paratherapeutic jaundice, who died of confluent bronchopneumonia (case 1). According to evidence derived from tests of hepatic function, identical parenchymatous damage occurs in cases of catarrhal jaundice, acute yellow atrophy and benign and fatal paratherapeutic jaundice, with only slight qualitative differences. This was emphasized by Geronne,<sup>14</sup> Strauss and Buerkmann,<sup>15</sup> Wolf,<sup>16</sup> Queyrat,<sup>17</sup> Lewin<sup>18</sup> and Kirch and Freundlich<sup>19</sup> and was also confirmed in the cases observed during the course of this study. It would, in fact, be as unreasonable to regard lobar pneumonia in cases with recovery as totally different from lobar pneumonia in fatal cases as to conceive a different pathologic process and pathogenesis for benign and fatal paratherapeutic icterus. Therefore, one may state that benign jaundice occurring in persons with syphilis represents the same condition as mild acute or subacute yellow atrophy. This does not deny that the condition in certain epidemics of catarrhal jaundice may be cholangitis, as Cantacuzene<sup>20</sup> asserted. However, those who, like McDonald,<sup>21</sup> believe paratherapeutic jaundice to be infectious, usually incriminating bacteria of the colon-typhoid group, submit evidence depending on the results of postmortem cultures of the blood, bile and liver tissue. Without adequate controls these results are worthless, as shown by the studies of Epstein and Kugel.<sup>22</sup> Moreover, Libman<sup>23</sup> observed in cases of parenchymatous degeneration of

14 Geronne, A. Zur Pathogenese einiger Formen des Ikterus (Ein Beitrag zur Frage des Leucins und Tyrosins), *Klin Wchnschr* **1** 828, 1922.

15 Strauss, L., and Buerkmann, W. Der Einfluss des Salvarsans auf die Bilrubinreaktion im Blutserum bei Lueskranken, zugleich ein Beitrag zur Frage der Salvarsanschädigungen, *Klin Wchnschr* **1** 1407 (July 8) 1922.

16 Wolf, M. Leberfunktion bei Lues und ihre Bedeutung zur Verhütung von Salvarsanschaden, *Dermat Ztschr* **42** 169, 1924.

17 Queyrat, M. L. Salvarsan et neosalvarsan, de quelques reactions du foie consecutives a leur injection, meiotragie hepatique a type urobilurique, *Bull et mem Soc med d hôp de Paris* **38** 299, 1914.

18 Lewin, E. M. Neues zur Lehre von der toxischen Wirkung der Arsenbenzolpräparate auf die Leber, *Arch f Dermat u Syph* **159** 77, 1929.

19 Kirch, A., and Freundlich, J. Zur Frage der Leberschädigung bei Lues und Salvarsantherapie, *Arch f Dermat u Syph* **136** 107, 1921.

20 Cantacuzene, J. Sur une epidemie d'ictère observee en Roumanie pendant la campagne de 1917, *Presse med* **26** 541, 1918.

21 McDonald, S. Acute Yellow Atrophy in Syphilis, *Brit M J* **1** 76, 1918.

22 Epstein, E. Z., and Kugel, M. A. The Significance of Postmortem Bacteriological Examination, *J Lab & Clin Med* **44** 327, 1929.

23 Libman, E. On Some Experiences with Blood Cultures in the Study of Bacterial Infections, *Bull Johns Hopkins Hosp* **17** 215, 1926.

the liver of unknown etiology that cultures of the blood made during life were sterile

The purpose of the study reported here was to investigate the relation of arsphenamine therapy to jaundice. Thirty-one cases have been observed, and the literature has been studied

#### RELATION OF DEFINITE ANATOMIC SYPHILIS OF THE LIVER TO JAUNDICE

Slight transient jaundice may be encountered in cases of syphilitic cirrhosis, but neither this condition nor gumma of the liver gives the familiar picture of benign or fatal jaundice. In my records there were twelve cases of gumma of the liver, syphilitic cirrhosis or *hepar lobatum*, in only one instance was jaundice present, and in that case it was faint and transient. Wile and Sams<sup>24</sup> reported similar observations.

A careful search of the records of the cases of tertiary syphilis of the liver with necropsy observations reported by Murchison,<sup>25</sup> Legg,<sup>26</sup> Fournier,<sup>27</sup> Frerichs,<sup>28</sup> McCrae and Caven<sup>29</sup> and other observers, both before and after the introduction of arsphenamine, failed to reveal in a single case a condition which will fit into the picture of acute yellow atrophy. Nor are the clinical pictures of the two diseases alike. On the other hand, lesions in cases of fatal paratherapeutic icterus are always those of acute or subacute yellow atrophy or coarse nodular cirrhosis, the familiar lesions of hepatic syphilis are uniformly absent, and spirochetes are never found, as pointed out by Ravaut<sup>30</sup> and Fischer<sup>31</sup> and as mentioned in the following section. Even if gumma or syphilitic cirrhosis should be found in association with acute yellow atrophy, the etiologic relation of the two would not thereby be proved. But I am aware of no case in which this association was present.

24 Wile, U. J., and Sams, W. M. A Study of Jaundice in Syphilis. Its Relation to Therapy, *Am J M Sc* **187** 297 (March) 1934.

25 Murchison, C. Clinical Lectures on Diseases of the Liver, London, Longmans, Green & Company, 1874.

26 Legg, J. W. Bile, Jaundice, and Bilious Diseases, London, H. K. Lewis, 1880.

27 Fournier, A. Traite de syphilis, Paris, J. Rueff, 1906, vol. 2, pt. 2.

28 Frerichs, F. T. A Clinical Treatise of Diseases of the Liver, London, New Sydenham Society, 1860.

29 McCrae, T. Tertiary Syphilis of the Liver, *Am J M Sc* **144** 625 (Nov.) 1912. McCrae, T., and Caven, W. R. Tertiary Syphilis of the Liver, *Am J M Sc* **172** 781 (Dec.) 1926.

30 Ravaut, P. Pathogenesis and Therapy of Para-Arsenical Icterus, *Bull Soc franç de dermat et syph* **35** 818, 1928, in discussion, *ibid* **35** 237 and 887, 1928, Ictère survenu deux mois après un traitement arsenicomercurel. Ictère grave. Mort, *ibid* **28** 57, 1921.

31 Fischer, B. Ueber Todesfälle nach Salvarsan, *Deutsche med Wchnschr* **41** 908, 939 and 976, 1915.

Therefore, it can be definitely asserted that there is no proved relation between anatomic tertiary syphilis of the liver and paratherapeutic jaundice

#### RÔLE, OF THE ARSPHENAMINES IN THE CAUSATION OF JAUNDICE

*1 Jaundice with Syphilis Before the Introduction of the Arspenamines*—Only one type of frank jaundice was associated with syphilis in the prearsphenamine era. This occurred in the secondary stage only and was called icterus syphiliticus praecox. Though known since the sixteenth century, an accurate description of the syndrome with and without acute yellow atrophy was not made until the nineteenth century. Portal<sup>32</sup> and Ricord<sup>33</sup> vaguely delineated it, then Gubler<sup>34</sup> (1856), followed by Lancereaux<sup>35</sup> and Lasch,<sup>36</sup> more thoroughly described its characteristics. Lebert<sup>37</sup> and Engel-Reimers<sup>38</sup> noted the occurrence of acute yellow atrophy as a complication. According to Werner's<sup>39</sup> extensive statistics, the disease occurred in 0.37 per cent of persons with syphilis in the secondary stage.

Icterus syphiliticus praecox, as noted previously, is a nonobstructive type of jaundice. It usually appears at the same time as the eruptive phenomena of the secondary stage but may precede or follow them by a short interval. Symptoms may appear shortly after the inception of treatment with mercury or bismuth, since these drugs do not manifest their therapeutic action as quickly as the arspenamines. The jaundice has occasionally been attributed to mercury, but there is no trustworthy evidence to substantiate this contention, as was pointed out long ago by Lebert<sup>37</sup> and more recently by Stokes and his associates<sup>40</sup>.

32 Portal, A. Observations sur la nature et le traitement des maladies du foie, Paris, Longchamps, 1813.

33 Ricord, P. Traite complet des maladies vénériennes, Paris, J. Rouvier, 1851.

34 Gubler, A. Memoire sur l'ictère qui accompagne les eruptions syphilitiques precoces, Compt rend Soc de biol (pt 2) 5 235, 1854.

35 Lancereaux, E. A Treatise on Syphilis, London, New Sydenham Society, 1868.

36 Lasch, O. Visceral Affections in the Early Stages of Syphilis. I. Icterus Syphiliticus Praecox, in Selected Essays and Monographs, London, New Sydenham Society, 1900, p 145, Berl Klin Wchnschr 31 904, 1894.

37 Lebert. Ueber Ikterus typhoïdes, Virchows Arch f path Anat 7 341, 1854-1855.

38 Engel-Reimers, J. Akute gelbe Leberatrophie in der Fruhperiode der Syphilis, Jahrb d Hamb Straatskrankenanst 1 325, 1889.

39 Werner, S. Beitrage zur Pathologie des Ikterus syphiliticus, Munchen med Wchnschr 44 736, 1897.

40 Stokes, J. H., Reudemann, R. J., and Lemon, W. S. Epidemic Infectious Jaundice and Its Relation to the Therapy of Syphilis, Arch Int Med 26 521 (Nov) 1920.

When insufficient treatment has been given jaundice may appear as part of a generalized secondary recurrence in association with the typical cutaneous and mucosal phenomena and a positive reaction to the Wassermann test—facts which must be emphasized Gennerich,<sup>41</sup> Ruge<sup>42</sup> and Fuhs and Weltmann<sup>43</sup> reported many cases, all of which clearly establish these criteria for the recognition of icterus syphiliticus praecox as a complication of a recurrence of secondary syphilis following inadequate treatment

The prognosis in cases of icterus syphiliticus praecox is generally good, the condition usually running the benign course of catarrhal jaundice. However, approximately 10 per cent of patients die of acute yellow atrophy (Engel-Reimers,<sup>38</sup> Weber<sup>44</sup>)

Investigation of postmortem material has thus far failed to reveal *Spirochaeta pallida* in the liver, although sections of the skin made simultaneously may have shown spirochetes in profusion (Fuhs and Weltmann,<sup>43</sup> Buraczynski,<sup>45</sup> Veszpremi and Kanitz,<sup>46</sup> Schmorl,<sup>47</sup> Buschke and Michael,<sup>48</sup> Bierring,<sup>49</sup> Severin and Heinrichsdorff,<sup>50</sup> Herxheimer and Gerlach<sup>51</sup>) Inoculations of hepatic tissue into animals have likewise given negative results. Only Warthin<sup>52</sup> succeeded in demonstrating spirochetes in the liver of a patient with icterus syphiliti-

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41 Gennerich, W. Der Behandlung der Syphilis mit Salversanpräparaten, *Ergebn d inn med u Kinderh* **20** 368, 1921

42 Ruge, H. Zehn Jahre Gelbsucht in der Marine (1919-1929), *Beobachtungen an 2,500 Fällen*, *Ergbn d inn Med u Kinderh* **41** 1, 1931

43 Fuhs, H., and Weltmann, O. Ueber Ikterus bei Lues, *Arch f Dermat u Syph* **140** 247, 1922

44 Weber, F. P. Acute Hepatic Atrophy in Early or Secondary Syphilis, *Proc Roy Soc Med (Path Sect)* **2** 116, 1909

45 Buraczynski, A. Ikterus im Frühstadium der Lues, *Wien klin Rundschau* **21** 651, 1907

46 Veszpremi, D., and Kanitz, H. Akute gelbe Atrophy bei Lues 2, *Arch f Dermat u Syph* **88** 35, 1907

47 Schmorl. Pathologic Demonstrations, *München med Wchnschr* **69** 908, 1922

48 Buschke, A., and Michael. Salvarsanwirkungen, *Berl klin Wchnschr* **51** 1935, 1914

49 Bierring, K. Totliche Lebersyphilis, *Zentralbl f Haut- u Geschlechtskr* **7** 411, 1922

50 Severin and Heinrichsdorff. Zur Frage der Leberveränderungen nach Salvarsan, *Ztschr f klin Med* **76** 128, 1912

51 Herxheimer, G., and Gerlach, W. Ueber Leberatrophie und ihre Verhältnisse zu Syphilis und Salvarsan, *Beitr z path Anat u z allg Path* **68** 93, 1921

52 Warthin, A. S. The New Pathology of Syphilis, *Am J Syph & Neurol* **2** 425, 1918

cus praecox (one case) However, his report lacks detail, and his observations are at variance with those of all other investigators in the field

The conclusion, therefore, is strongly suggested that the jaundice in untreated persons with secondary syphilis is caused by parenchymatous hepatic injury effected indirectly by the spirochete through the toxemia associated with its generalization and that it is not caused by an inflammatory reaction of the liver to the spirochete itself Most of the investigators cited earlier agreed with this conception It is also in accord with the demonstration by Babalian,<sup>53</sup> Sade,<sup>54</sup> Kleeberg,<sup>55</sup> Kirch and Freundlich<sup>19</sup> and others that tests of function reveal hepatic damage in a considerable proportion of cases of secondary syphilis without jaundice

2 *Comparison of Incidence of Jaundice with Syphilis Before and After the Introduction of Arsphenamine*—With the era introduced by Ehrlich in 1910, jaundice as a complication of syphilis or its treatment assumed significant proportions not only in the secondary but also in the tertiary stage of the disease Although paratherapeutic icterus did not gain wide notice in Europe until the period of the World War and in America until later, the number of cases reported before the war was considerable The first cases were described in 1910 Dujardin,<sup>56</sup> of Brussels, in January 1914 stated that he had observed twenty-five cases following the use of neoarsphenamine Jaundice, which before the introduction of arsphenamine had been estimated as a complication in 0.37 per cent of the cases of secondary syphilis and in none of the cases of tertiary syphilis, was now a frequent occurrence in both phases of the disease Reports from almost every country show a considerable incidence of paratherapeutic icterus Cole and his associates<sup>57</sup> in the United States estimated it at about 2 per cent of cases in which treatment had been given, and Scott and Pearson<sup>58</sup> in Canada estimated it

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53 Babalian Les retentions biliaires latentes des syphilitiques, Bull Soc franç de dermat et syph **35** 870, 1928

54 Sade, I Die Leberfunktionprüfungen bei Syphilis und Salvarsanikterus, Zentralbl f Haut- u Geschlechtskr **23** 62, 1927

55 Kleeberg, L Ueber Leberfunktionsprüfungen bei Lues, Med Klin **16** 1162, 1920

56 Dujardin, B Les ictères toxiques dus au neo-salvarsan, Clinique, Brussels **28** 103, 1914

57 Cole, H N, De Wolf, H, McCluskey, J M, Miskjian, H F, Williamson, G S, Rauschkolb, G R, Ruch, R O, and Taliaferro, C Toxic Effects Following Use of the Arsphenamines, J A M A **97** 897 (Sept 26) 1931

58 Scott, G O, and Pearson, G H J A Preliminary Report on Syphilitic and Arsenical Jaundice, Am J Syph & Neurol **3** 628, 1919

at about the same figure. Other estimates were as follows: Filliol<sup>59</sup> in France, 77 per cent, Milian and his co-workers,<sup>60</sup> about 20 per cent, Ruge<sup>42</sup> (incidence in the German marine corps), about 19 per cent, Gutmann,<sup>61</sup> 74 per cent, Gerrard<sup>62</sup> (incidence in the British navy), 46 per cent, Gorodetzky and Nartzisoff<sup>63</sup> in Russia, 25 per cent, and Gjessing<sup>64</sup> in Sweden, 1 per cent.

It is particularly illuminating to compare McCrae's<sup>29</sup> 1912 and 1926 reports on tertiary syphilis of the liver. While in the former there was no mention of a case in which the conditions simulated catarrhal jaundice, in the latter it was necessary to specify that such cases had been excluded because the patients had all received arsphenamine. A similar impression is obtained from the reports of MacLean,<sup>65</sup> McDonagh,<sup>66</sup> McDonald,<sup>21</sup> Gottron,<sup>67</sup> Brocq<sup>68</sup> and O'Leary, Greene and Rowntree<sup>69</sup>. Another change was noted by Heinrichsdorff<sup>70</sup> in the incidence according to sex. Previously icterus syphiliticus praecox had been predominant in females by two to one. Paratherapeutic icterus, however, usually predominates in males.

These changes, which directly followed the introduction of arsphenamine in the frequency and the character of involvements of the liver in persons with syphilis, are so striking and definite that only arsphenamine can be held responsible for them.

*3 Experimental Evidence of the Hepatotoxic Action of the Arsphenamines*—Arsenic may be demonstrated in the liver and in the

59 Filliol, L. Les ictères au cours de traitements arsenobenzoliques, *Arch dermat-syph de clin de l'hôp St Louis* **2** 597, 1930.

60 Milian, G., Lotte, and Delarue. L'ictère paratherapeutique, *Bull Soc franç de dermat et syph* **35** 873, 1928.

61 Gutmann, C. Erfahrungen über Ikterus bei Syphilitikern, *Dermat Ztschr* **37** 39, 1922.

62 Gerrard, W. I. The Recognition of Latent Jaundice During Treatment with Arsenobenzol Compounds, *Brit M J* **2** 224, 1924.

63 Gorodetzky, A., and Nartzisoff. Course and Diagnosis of Late Arsphenamine Jaundice, *Venerol dermat* **7** 25, 1930.

64 Gjessing, H. C. Syphilis, Salvarsan, and Paratherapeutic Jaundice, *Acta dermat venerol* **11** 479, 1930.

65 MacLean, H. Arsenobenzol Treatment of Syphilis, *Brit M J* **2** 944, 1921.

66 McDonagh, J. E. R. Acute Yellow Atrophy in Lues, *Brit M J* **1** 189, 1918.

67 Gottron. Akute gelbe Leberatrophie bei mit Salvarsan behandelten Syphilitikern, *Dermat Ztschr* **35** 300, 1921-1922, **36** 225, 1922.

68 Brocq, L. Syphilitiques traités par les injections intraveineuses des nouveaux composés arsenicaux, *Bull med, Paris* **35** 235, 1921.

69 O'Leary, P., Greene, C. H., and Rowntree, L. Diseases of the Liver. Various Types of Syphilis of the Liver with Reference to Tests for Hepatic Function, *Arch Int Med* **44** 155 (Aug) 1929.

70 Heinrichsdorff. Leber-Lues, Salvarsan, Virchows *Arch f path Anat* **240** 441, 1922-1923.

urine of both man and animals after an injection of arsphenamine, as many observers (Wilcox,<sup>71</sup> Ullmann,<sup>72</sup> Policard and Pinard,<sup>73</sup> Tachau,<sup>74</sup> Morel and his co-workers<sup>75</sup>) have demonstrated. However, since arsenic may also be observed in the liver of a person in whom jaundice does not develop, even though treated with arsphenamine, these facts are not of striking significance.

On the other hand, laboratory animals suffer from focal hepatic necrosis and often from functional impairment when an arsphenamine preparation is injected. This has been repeatedly demonstrated by Voegtlin,<sup>76</sup> Hooper and his associates,<sup>77</sup> Morel and his associates,<sup>75</sup> Kolmer and Lucke<sup>78</sup> and others. Jaundice in animals has been difficult to induce, but Kolle,<sup>79</sup> Hooper,<sup>77</sup> Craven<sup>80</sup> and Schiffrin<sup>81</sup> succeeded in doing so by administering huge doses of arsphenamine to dogs.

*4 Relation of the Incidence of Jaundice to the Quantity of the Drug Given*—The relation of the quantity of a drug administered to the effect produced is usually difficult to demonstrate, because idiosyn-

71 Wilcox, W. A. Arsenobenzol Treatment of Syphilis, *Brit M J* **2** 944 1921, *Lancet* **1** 869, 1919.

72 Ullmann, K. Ueber Ausscheidungswerte und Speicherungsverhältnisse nach Einfuhr von Salvarsan in dem menschlich-tierschen Organismus, *Arch f Dermat u Syph* **114** 511, 1912.

73 Policard, A., and Pinard, J. A propos de la question des ictères au cours du traitement arsenical de la syphilis. Un cas d'ictère grave mortel avec dosage de l'arsenic dans le foie, *Paris med* **39** 42, 1921.

74 Tachau. Zur Kritik des Salvarsanikterus, *Deutsche med Wchnschr* **47** 677, 1921.

75 Morel, A. Mouriquand, G., and Policard, A. Le "606," le foie, et le rein, *Lyon med* **118** 1340, 1912, *Bull et mem Soc med d hop de Paris* **37** 402, 1914.

76 Voegtlin, C. The Pharmacology of Arsphenamine and Related Arsenicals, *Phys Rev* **5** 63, 1925.

77 Hooper, C. W., Kolls, A. C., and Wright, K. D. The Influence of Fasting, and Various Diets on Arsphenamine Poisoning, and the Comparative Toxicity of Arsphenamine, Neoarsphenamine and Para-ox-yaminophenylarsenoxide, *J Pharmacol & Exper Therap* **18** 133, 1921.

78 Kolmer, J. A., and Lucke, B. A Study of the Histological Changes Produced Experimentally in Rabbits by Arsphenamine, *Arch Dermat & Syph* **3** 483 (April) 1921, A Study of the Histologic Changes Produced Experimentally in Rabbits by Neoarsphenamine, *ibid* **3** 515 (April) 1921, A Study of the Histologic Changes Produced Experimentally in Rabbits by Mercurial Compounds, *ibid* **3** 531 (April) 1921.

79 Kolle, W. Experimentelle Studien zu Ehrlichs Salvarsantherapie der Spirochätenkrankheiten und über neue Salvarsanpräparate, *Deutsche med Wchnschr* **44** 1177 and 1211, 1918.

80 Craven, E. B., Jr. Importance of Diet in Preventing Acute Yellow Atrophy During Arsphenamine Treatment, *Bull Johns Hopkins Hosp* **48** 131 (March) 1931.

81 Schiffrin, A. Der Einfluss qualitativ verschiedener Ernährungsformen auf die durch Salvarsan hervorgerufene Lebernekrose, *Virchows Arch f path Anat* **287** 175, 1932.

crazy (using this term in its widest sense) may be involved. For instance, Biele,<sup>82</sup> Taege<sup>83</sup> and Weigeldt<sup>84</sup> reported cases in which a huge single or total dose of arsphenamine was given without producing jaundice. On the other hand, Hyman<sup>85</sup> and Lane<sup>86</sup> reported cases in which jaundice occurred after a single conservative dose. Nevertheless, Bodin,<sup>87</sup> Brodier<sup>88</sup> and Laurent<sup>89</sup> were able to show in large series of cases that the incidence of jaundice varied directly with the size of the dose. Arndt,<sup>90</sup> Friedmann,<sup>91</sup> Heller<sup>92</sup> and other syphilologists have reported a decrease in the incidence of jaundice following a reduction of the size of the routine dose. Recently the highest incidence has been reported from France, where, in general, vigorous treatment is practiced.

Simon<sup>93</sup> attributed the jaundice to excessively toxic batches of the drugs. But the fact that jaundice has occurred so universally with all brands and with numerous separate batches of the same brand is a strong argument against the assumption that faulty manufacture of the drug plays a considerable rôle.

*5 Association of Jaundice with Other Toxic Manifestations of the Arsphenamines*—An objection often leveled against the theory of the toxic etiology of paratherapeutic icterus is the frequent absence of other toxic reactions to arsphenamine. That such additional reactions may be absent is not surprising, since one seldom sees multiple toxic effects associated with arsphenamine dermatitis or with encephalitis associated

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82 Biele, K. Zur Dosierung des Salvarsans, *Deutsche Med. Wchnschr.* **47** 619 (June 2) 1921.

83 Taege, K. Zur Giftigkeit des Salvarsans, *München med. Wchnschr.* **67** 606, 1920.

84 Weigeldt, W. Zur Dosierung des Salvarsan, *Deutsche med. Wchnschr.* **46** 1193, 1920.

85 Hyman, A. S. Fatal Postarsphenamine Jaundice, *New York M. J.* **112** 496, 1920.

86 Lane, J. E. Discussion on Recent Developments in the Recognition and Treatment of Syphilis, *Brit. M. J.* **2** 673, 1911.

87 Bodin, E. Les ictères par le neosalvarsan, *Bull. Soc. franç. de dermat. et syph.* **28** 242, 1921.

88 Brodier, L. Note sur l'ictère de l'arsenobenzol, *Ann. d. mal. ven.* **15** 465, 1920.

89 Laurent, C. Les ictères des syphilitiques traités par le novarsenobenzol, *J. d. med. de Lyon* **2** 1367, 1921.

90 Arndt. Salvarsanfrage, *Med. Klin.* **18** 231, 1922.

91 Friedmann, M. Ueber Gelbsucht bei Syphilis während der Neosalvarsanbehandlung, *Dermat. Ztschr.* **26** 317, 1918.

92 Heller, J., in discussion on Gottron<sup>67</sup>.

93 Simon, C., in discussion on Sezary, M. Apropos de la pathogenie et du traitement des ictères paraarsénicaux, *Bull. Soc. franç. de dermat. et syph.* **35**: 883, 1928.



with arsphenamine therapy and since sensitivity of one tissue or organ without a reaction on the part of the others is observed in many other fields of medicine

Nevertheless, the number of cases of multiple toxic phenomena observed is considerable. Arsphenamine dermatitis is the most common toxic accompaniment of jaundice, but aplastic anemia, agranulocytic, leukopenic and monocytic reactions of the hematopoietic system and polyneuritis are not rare. Among my cases was one of monocytic angina, previously reported by Rosenthal,<sup>94</sup> and one of secondary anemia and leukopenia. Cole and his associates<sup>57</sup> reported two cases in which the condition was complicated by arsphenamine dermatitis, in one of which aplastic anemia also occurred. The literature contains many reports of cases with dual toxic phenomena.

*6 Jaundice in Nonsyphilitic Patients Treated with the Arsphenamines*—It is not uncommon to encounter jaundice as a complication of the treatment of nonsyphilitic diseases with arsphenamine. Filliol<sup>59</sup> put the figure at 1.75 per cent. I have records of three such accidents—one in a case of chronic iritis, one in a case of multiple sclerosis and the third as the result of specific treatment in a case of syphilophobia. Sicard and his collaborators,<sup>95</sup> who first described paratherapeutic icterus without syphilis, reported two such cases. Bernheim,<sup>96</sup> Lindstedt,<sup>97</sup> Nast<sup>98</sup> and others have also reported cases. Ruge<sup>42</sup> reported fifty-two cases, however, many of his patients suffered from malaria or other diseases that might possibly be associated with jaundice.

The possibility that the condition in these cases may have represented intercurrent attacks of catarrhal jaundice will be discussed later. The assumption, however, is strongly indicated that arsphenamine was the sole cause.

*7 Relation of Jaundice Following Treatment with the Arsphenamines to Active Syphilis of the Liver, the Heirheimer Reaction and So-Called Hepatonecroses*—Concerning the jaundice occurring during the active treatment of syphilis with the arsphenamines (early icterus), there is ample reason to exclude syphilis as the cause. It is hardly credible that syphilitic involvement of the liver should progress

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94 Rosenthal, N. Leucopenic Infectious Monocytosis, in Libman Anniversary Volumes, New York, International Press, 1932, vol. 3, p. 1003.

95 Sicard, Haguénau and Kudelski. Traitement de la syphilis nerveuse chronique. Les éléments de contrôle de la médication novarsenicale, Bull. et mem. Soc. med. d. hop. de Paris **43** 833, 1919.

96 Bernheim, E. Syphilis-Ikterus-Salvarsans, Deutsche Med. Wchnschr. **51** 904 (March 29) 1925.

97 Lindstedt, F. Ueber "Salvarsan Ikterus" und dessen Verhältnisse zum "katarrhalischen" und syphilitischen Ikterus, Acta med. Scandinav. **59** 209, 1923.

98 Nast, in discussion, Dermat. Wchnschr. **69** 505, 1919.

under treatment with arsphenamine while other syphilitic phenomena disappear. Furthermore, many patients already have a negative Wassermann reaction by the time the jaundice appears.

Some physicians regard the rare reaction which follows the first or second injection as a Herxheimer reaction, but even here, the considerations just mentioned, as well as the fact that spirochetes have never been demonstrated in the livers of patients dying of arsphenamine jaundice, make this seem improbable. Milian's concept of biotropism, i. e., that bactericidal drugs may somehow enhance the virulence of localized organisms, is too speculative to be accepted without further evidence.

Jaundice occurring after a lapse of treatment with the arsphenamines (late icterus) has been regarded by many as a recurrence of active syphilis affecting the liver only (so-called hepatorecurrence or monohepatorecurrence). The evidence against this conception is overwhelming. One finds that the patients have almost uniformly received adequate treatment, the reaction to the Wassermann test is often negative, and the jaundice never has been reported as occurring with manifestations of active syphilis. Indeed, Gennerich<sup>41</sup> stated pointedly that an isolated syphilitic hepatorecurrence is never encountered. He insisted, with justice, that the last organ to give evidence of a syphilitic relapse is the liver, and that when this involvement of the liver does occur there are always a well marked exanthem, a positive Wassermann reaction and a history of insufficient treatment. The condition in these cases is therefore to be considered as icterus syphiliticus praecox. The condition in all of Ruge's<sup>42</sup> and Fuhs' and Weltmann's<sup>43</sup> cases conformed to this formula. As for the so-called hepatorecurrences in cases of tertiary syphilis, one would hardly expect to see a relapse from the tertiary into the secondary stage. Moreover, Gutmann<sup>61</sup> did not encounter a single case of late icterus with any evidence of active syphilis in a series of seventy-five cases.

Paratherapeutic icterus, therefore, cannot be considered as a manifestation of active syphilis of the liver in any form, recurrent or otherwise.

8 *Certain Arguments Usually Brought Against the Arsphenamine Etiology of Jaundice*—Latent Period Associated with Late Icterus (a) Time relationships. One of the chief obstacles to the acceptance of late icterus as a product of the toxicity of arsphenamine is the difficulty in believing that a drug could cause its toxic manifestation long after the last dose was given. The opinion that it is an active syphilitic hepatorecurrence has already been discussed. Another view often maintained is that late icterus is merely catarrhal jaundice, which has accidentally attacked a syphilitic patient who has been treated with the arsphenamines. The chronological curve of the incidence of late icterus,

as shown by many long series of cases, reaches a peak from the fourth to the eighth week after the last antisyphilitic injection and then falls off to the ninth or tenth month. If late icterus were in truth, accidental catarrhal jaundice, there would be just as many cases occurring twenty months after the last injection as two months after. Probably only the few scattered cases of jaundice that do occur after the tenth month are fortuitous cases of catarrhal jaundice. This definite curve of incidence therefore indicates a real relationship between late icterus and the previous administration of arsphenamine.

Late icterus, it should be noted, represents as much as 70 per cent of the cases of paratherapeutic jaundice (Ruge). In the small series of cases analyzed here it constituted 50 per cent.

(b) *Studies of hepatic function.* Although it is difficult to trace the course of hepatic degeneration by tests of the function of the liver, if judiciously studied the results do not fail to bring important, even if limited, indications that the injection of arsphenamine may be followed by hepatic damage even when jaundice is not produced. Wallis,<sup>99</sup> using the test for lipase in the blood, which according to the early work of Quinan<sup>100</sup> and Whipple<sup>101</sup> (1913) seems to be well founded, was able to show that after arsphenamine therapy, even though jaundice was not produced, functional damage to the liver reached its maximum about two months after the last injection. The damage gradually receded to normal at about the sixth month after the injections were stopped. Wallis confirmed these results with the levulose tolerance test. Similar results were also obtained with Widal's hemoclastic crisis, which, however, is a test the reliability of which has been seriously questioned.

This evidence may be correlated with the work of Chargin and Orgel,<sup>102</sup> who observed the level of bilirubin in the blood during and after arsphenamine therapy. Of eighty-two patients, fourteen showed an elevation of the level of bilirubin in the blood in the absence of frank clinical jaundice, the elevation appearing from three to five weeks after the last injection of arsphenamine. Kloeppel<sup>103</sup> and Schneider confirmed these results. Indeed, it is known that severe degenerative hepatic disease may be present and may even cause death without the

99 Wallis, R. L. M. *Brit. M. J.* **2**: 944, 1921.

100 Quinan, C. *Lipase Studies*, *J. M. Research* **32**: 45 and 73, 1915.

101 Whipple, G. H. *A Test for Hepatic Injury: Blood Lipase*, *Bull. Johns Hopkins Hosp.* **24**: 357, 1913.

102 Chargin, L., and Orgel, S. Z. *Jaundice in Syphilitic Persons Receiving Arsenical Medication: Its Early Detection and Possible Prevention*, *Arch. Dermat. & Syph.* **7**: 495 (April) 1923.

103 Kloeppel, F. W. *Lues und Salvarsan in ihrem etiologischen Zusammenhang mit Icterus und Bilirubinämie*, *Klin. Wchnschr.* **1**: 2021 (Sept.) 1922, *Dermat. Ztschr.* **37**: 137, 1922.

appearance of jaundice (Bergstrand,<sup>104</sup> Rolleston and McNee<sup>105</sup>) A case described by Stewart, Vining and Bibby<sup>106</sup> illustrates this fact A girl, who was said to have had faint jaundice for two days after an injection of arsphenamine, died suddenly during a minor operation This took place three months after the last injection of arsphenamine, and at the time of death there was no jaundice Necropsy showed acute yellow atrophy

The considerations already enumerated point to the existence of latent damage to the liver after treatment with arsphenamine in a considerable percentage of cases, even in the absence of jaundice

(c) Analogy to the other hepatotoxins Analogy may serve further to mitigate one's incredulity, since delayed jaundice is not produced only by arsphenamine but may be caused by other hepatotoxins as well Tri-nitrotoluene, acetylene-tetra-chloride, di-nitrophenol and blue cross gas (di-phenylchlorarsine) have produced late icterus The number of cases of tri-nitrotoluene poisoning that occurred several months after the victims had severed all connections with munitions factories is fairly large Also, experimentally, Mallory and Parker<sup>107</sup> noted that in cases of acute copper poisoning the maximal hepatic damage does not appear immediately but is delayed more than two weeks

Thus, the definite time relationship, the evidence of functional tests and the analogy to other hepatotoxins point to the etiologic importance of the arsphenamines in cases of late icterus

Disappearance of Jaundice Following the Use of Arsphenamine While More Arsphenamine Is Being Given (a) Analogy drawn from experimental pathologic changes in the liver The most impregnable defense of those who have asserted the syphilitic etiology of arsphenamine jaundice is the fact that the jaundice may disappear during the continued administration of arsphenamine, a point stressed particularly by Milian, Lotte and Delarue,<sup>57</sup> Wosegien,<sup>6</sup> Fabry<sup>108</sup> and their followers, who assumed that thereby the syphilis of the liver was cured Many have expressed the opinion that this argument is false, since it is well known that the patient also recovers without any antisymphilitic treatment An adequate explanation of this paradox has not yet been advanced

104 Bergstrand, H Ueber die akute und chronische gelbe Leberatrophie mit besonderer Berücksichtigung ihres epidemischen Auftretens in Schweden im Jahre 1927, Leipzig, Georg Thieme, 1930

105 Rolleston, H, and McNee, J W Diseases of the Liver, Gall Bladder and Bile Ducts, New York, The Macmillan Company, 1929

106 Stewart, M J, Vining, C W, and Bibby, J P Subacute Yellow Atrophy in a Case of Syphilis Following Treatment with Galyol, J Path & Bact. **23** 120, 1919

107 Mallory, F B, and Parker, F, Jr Experimental Copper Poisoning, Am. J Path **7** 351 (July) 1931

108 Fabry, H Spätikterus nach Salvarsan, Med Klin **14** 260, 1918

Nevertheless, there are certain observations on the experimental pathologic changes of the liver which yield suggestive intimations of the mechanism of this paradoxical disappearance of arsphenamine jaundice under continued specific therapy. Anderson<sup>109</sup> and Lacquet,<sup>110</sup> co-workers of F. C. Mann, performed partial hepatectomy on rats and observed that the newly regenerated hepatic tissue was less easily and less extensively damaged by chloroform and carbon tetra-chloride than the normal liver. This observation is of the utmost significance, for postmortem examinations have shown that acute yellow atrophy without some evidence of regeneration and hyperplasia of the liver is uncommon. Therefore, when one gives arsphenamine to a patient with paratherapeutic icterus, the drug meets not only the same liver tissue that was present on previous injections but a regenerating or newly regenerated tissue different in many respects from its parent tissue—different in the content of glycogen, fat and protein (Hashimoto and Pick<sup>111</sup>), different in its reactive potentialities and different perhaps in its sensitivity (Rossle<sup>112</sup>). That this regeneration actually occurs was seen clearly in case 1, in which death occurred accidentally during the healing stage of paratherapeutic icterus.

The experimental observations of Opie and Alford,<sup>113</sup> Quinan<sup>100</sup> and Davis and Whipple<sup>114</sup> support the theory just mentioned. These authors found that animals surviving the administration of hepatic poison could be given equally large doses of the poison shortly afterward without increasing the necrosis of the liver. Ogata,<sup>115</sup> using icterogen,

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109 Anderson, R. M. Experimental Pathology of the Liver. II. Effect of Chloroform on the Normal and on the Restored Liver Following Partial Removal, *Arch. Path.* **14** 335 (Sept.) 1932.

110 Lacquet, A. M. Effects of Carbon Tetrachloride on the Normal and on the Restored Liver After Partial Hepatectomy, *Arch. Path.* **14** 164 (Aug.) 1932.

111 Hashimoto, M., and Pick, E. P. Ueber den intravitalen Eiweissabbau in der Leber sensibilisierter Tiere und dessen Beeinflussung der Milz, *Arch. f. exper. Path. u. Pharmacol.* **76** 89, 1914.

112 Rossle, R. Allergie und Pathergie, *Klin. Wchnschr.* **12** 574 (April 15) 1933.

113 Opie, E. L., and Alford, L. B. The Influence of Diet on the Toxicity of Substances Which Produce Lesions in the Liver and Kidney, *J. A. M. A.* **62** 895 (March 21) 1914. Opie, E. L., Barker, B. I., and Dochez, A. R. Change in the Proteolytic Enzymes and Anti-Enzymes of the Blood Serum Produced by Substances (Chloroform and Phosphorus) Which Cause Degenerative Changes in the Liver, *J. Exper. Med.* **13** 162, 1911.

114 Davis, N. C., and Whipple, H. G. Effect of Fasting and Various Diets on Liver Injuries Effected by Chloroform Poisoning, *Arch. Int. Med.* **23** 612 (May) 1919.

115 Ogata, T. Beiträge zur experimentell erzeugten Lebercirrhose und zur Pathogenese des Ikterus mit spezieller Berücksichtigung der Gallencapillaren bei der Unterbindung des Ductus choledochus und der Ikterogenvergiftung, *Beitr. z. path. Anat. u. z. allg. Path.* **55** 236, 1913.

a powerful hepatotoxic organic arsenical preparation, noted that surviving poisoned rats, even while jaundiced, were unaffected by repeated injections of ordinarily lethal doses of the same poison. Schiffrin,<sup>81</sup> in experiments with sodium arsphenamine, observed that in a dog in which jaundice had developed icterus did not recur when a larger dose was given one week later. Thus, it is evident that in animals under control conditions, even with arsphenamine poisoning, phenomena occur which are analogous to the paradoxical innocuousness of arsphenamine used in the treatment of paratherapeutic jaundice.

That young cells may be more resistant to hepatic poisons was also indicated by the work of Whipple<sup>116</sup> (1912). He noted that the livers of young pups were resistant to chloroform poisoning. This was later attributed by Graham<sup>117</sup> to the high glycogen content of their livers.

It must also be noted that Love,<sup>118</sup> another co-worker of Mann, obtained results contrary to those of Anderson and Lacquet. Using phosphorus instead of chloroform and carbon tetra-chloride, he found that phosphorus damaged the regenerated tissue more than the normal tissue. This observation neither denied the results of Anderson and Lacquet, who used chloroform and carbon tetra-chloride, nor destroyed my analogy, but it did emphasize the complexity of hepatic reactions. The explanation of these atypical reactions is probably connected with the fact that phosphorus causes fatty changes and necrosis in the periphery of the liver lobule, while chloroform, carbon tetra-chloride and the arsphenamines which cause acute yellow atrophy destroy chiefly the central and middle portions of the lobule.

(b) Untoward accidents and recurrences of the jaundice. The mechanism just described is not always sufficient to protect the liver from the toxic effects of further treatment with arsphenamine. Contrary to the many reports of Milian, one may not recklessly continue the injection of arsphenamine in cases of paratherapeutic jaundice. Not only have a number of deaths occurred after such procedure but patients who had been doing well on nonspecific therapy have had a relapse on the resumption of treatment with arsphenamine. Milian and his associates,<sup>60</sup> reported that in four of ninety-three cases of paratherapeutic icterus in which neoarsphenamine was administered there were fatal results, which they attributed vaguely to certain accidental factors. The condition in Ravaut's<sup>30</sup> cases was more definite.

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116 Whipple, G. H. Insusceptibility of Pups to Chloroform Poisoning During the First Three Weeks of Life, *J. Exper. Med.* **15** 259, 1912.

117 Graham, E. A. Resistance of Pups to Late Chloroform Poisoning in Its Relation to Glycogen, *J. Exper. Med.* **21** 185, 1915.

118 Love, J. G. The Effect of Phosphorus on the Normal and on the Restored Liver Following Partial Hepatectomy, *Arch. Path.* **14** 637 (Nov.) 1932.

Twice coming under Milian's influence, he was twice compelled to renounce Milian's methods because of fatal results Sicard<sup>95</sup> reported the case of a patient with paresis in whom icterus developed during treatment Further specific therapy, though ordered to be stopped, was by accident continued, the result was death of acute yellow atrophy Chargin and Orgel<sup>102</sup> caused frank jaundice to appear by continuing to treat three patients in whom during arsphenamine therapy latent icterus had already developed, according to the estimation of the bilirubin content of the blood Schneider,<sup>119</sup> Geirard<sup>62</sup> and Dixon, Campbell and Hanna<sup>120</sup> had similar experiences Todd<sup>121</sup> also expressed the opinion that jaundice is aggravated by the continuation of treatment with arsphenamine Nicaud<sup>122</sup> reported three cases in which the condition either grew worse or recurred after therapy was resumed, one patient suffering four relapses Leredde and Kuene-mann<sup>123</sup> reported a case in which jaundice recurred six times before treatment with arsphenamine was finally abandoned Laurent,<sup>89</sup> Stumpke<sup>124</sup> and Wechselmann and Hohorst<sup>125</sup> had similar experiences One of my patients had two attacks of paratherapeutic icterus ten years apart These reports gain greater significance from the consideration of the following facts (1) I have not been able to find in the literature a record of a relapse with nonspecific therapy, (2) there were no deaths (save in case 1) or recurrences in the thirty-one cases I observed, although all the patients were treated with nonspecific therapy, with the addition of bismuth in a few instances

*9 Relation of Jaundice Following Arsphenamine Therapy to Epidemic or Endemic Catarrhal Jaundice*—It remains now to consider the problem of the identity of paratherapeutic icterus with epidemic or endemic catarrhal jaundice No definite evidence of such an identity has yet been presented However, Stokes, Reudemann and Lemon,<sup>40</sup> Ruge<sup>42</sup> and many others have expressed the opinion that the increase

119 Schneider, P Untersuchungen uber den Bilirubingehalt bei Salvarsan-quecksilber, *Dermat Wchnschr* **74** 228 and 250, 1922

120 Dixon, H A , Campbell, W R , and Hanna, M I Control of Arsphenamine Treatment by Liver Function Tests, *Canad M A J* **16** 551 (May) 1926

121 Todd, A T Post-Salvarsan Jaundice, *Lancet* **1** 632 (March 26) 1921

122 Nicaud, P Jaundice Following Treatment with Salvarsan and Neosalvarsan, *Presse med* **28** 322, 1920

123 Leredde and Kuenemann Les accidents de 606 et leurs causes Statistique de 416 injections intraveineuses, *Bull Soc franç de dermat et syph* **22** 449, 1911

124 Stumpke, G Zur Frage des Ikterus nach Salvarsan, *Med Klin* **18** 295, 1922

125 Wechselmann, W , and Hohorst, W Ueber den Einfluss der Salvarsanbehandlung auf den Bilirubingehalt des Blutserums, *Arch f Dermat u Syph* **136** 285, 1921

in the occurrence of paratherapeutic icterus is explained by a simultaneous increase in the occurrence of catarrhal jaundice. Epidemics of catarrhal jaundice are common, and they occurred with frequency before the era of arsphenamine therapy. Hennig<sup>126</sup> in 1890 reported eighty-six epidemics of jaundice in all quarters of the world during the preceding one hundred and ninety years, yet in none of these epidemics was an unusual proportion of syphilitic persons noted. However, if paratherapeutic icterus today is to be regarded as catarrhal jaundice, the proportion of syphilitic persons in the latter group would be astounding (approximately 20 per cent, according to my statistics).

Ruge, for instance, reported statistics on a large number of cases of jaundice in the German marine, which showed that the proportion of persons treated for syphilis who suffered from jaundice was approximately eight times greater than the general incidence of jaundice in the entire group. Todd<sup>121</sup> in 1921 reported statistics on the incidence of jaundice among the British troops on the Rhine, where catarrhal jaundice was endemic at the time. Of syphilitic soldiers treated with the arsphenamines, jaundice developed in 83 per cent, while only 0.3 per cent of the rest of the troops were affected.

Statistics at the Mount Sinai Hospital indicate that during the past five years the incidence of paratherapeutic jaundice among syphilitic persons was four times greater than the incidence of catarrhal jaundice and acute yellow atrophy among the patients on the general medical list.

Furthermore, as was pointed out before, the curve of incidence of cases of late icterus rules out the possibility of a chance intercurrent disease being responsible for the jaundice. Moreover, Zimmern<sup>127</sup> and Ruge<sup>42</sup> pointed out that during the World War the incidence of catarrhal jaundice in Germany did not increase remarkably, while the incidence of jaundice associated with arsphenamine therapy decidedly did. The graphic data of Muller<sup>128</sup> also show that catarrhal and arsphenamine jaundice did not predominate during the same periods.

There are other circumstances leading to the conclusion that catarrhal jaundice is not identical with paratherapeutic icterus. For instance, the severity of the jaundice, as measured by the proportion of cases of acute yellow atrophy, is generally greater in cases of paratherapeutic icterus than in cases of catarrhal jaundice, as demonstrated by the statistics of both Heinrichsdorff<sup>70</sup> and Ruge<sup>42</sup>. The series of

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126 Hennig, A. Ueber epidemischen Icterus, *Samml klin Vortr* no 8, 1890 (*Inn Med* no 4, p 77)

127 Zimmern, F. Spatikterus nach Salvarsan, *Dermat Ztschr* **27** 138, 1919

128 Muller, I. Zur Statistik der Lebererkrankungen im Zeitraum von Jan 1914 bis Marz 1922, *Klin Wchnschr* **1** 835, 1922



cases mentioned in the reports of the Medical Research Council<sup>129</sup> of Great Britain and the series reported by Silbergleit and Fockler<sup>130</sup> were attended by extremely high mortality. Kuznitsky and Fuchs<sup>131</sup> also expressed the opinion that the increase in the incidence of acute yellow atrophy following arsphenamine therapy was absolute and was not related to an increase in the incidence of catarrhal jaundice in recent years.

All these observations speak for the fundamental independence of paratherapeutic icterus and of catarrhal jaundice, although I shall later point out that the conditions may sometimes act together in summation or potentiation.

*10 Factors Which Predispose to the Occurrence of Arsphenamine Jaundice Endemic Catarrhal Jaundice, Malnutrition, Etc*—From the foregoing facts it is concluded that paratherapeutic icterus is caused fundamentally by the effect of the arsphenamines on the liver. The word fundamentally is emphasized because there are apparently other contributory or predisposing factors of definite, though less, importance, which may act with the arsphenamines as summing or potentiating agents.

Masson<sup>132</sup> demonstrated experimentally that if the liver of an animal is damaged by chloroform, the proportion of a subsequent dose of arsphenamine taken up by this injured liver will be greater than that taken up by the normal liver. Rossle<sup>112</sup> reported similar results. Thiroux and his associates<sup>133</sup> found that if sheep serum, which is extremely toxic to rabbits when injected intravenously, is injected subcutaneously no harmful effect is apparent. But, if this is followed by a dose of arsphenamine, jaundice and hepatic damage ensue. Control animals given horse serum and arsphenamine were unaffected. These experiments suggest that another hepatotoxic agent acting on the liver simultaneously with the arsphenamine may potentiate the effect of the latter.

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129 Reports of the Salvarsan Committee, Toxic Effect Following the Employment of Arsenobenzol Preparations, Medical Research Council, Special Report Series, no. 66, London, His Majesty's Stationery Office, 1922, Result of the Examination of the Tissues from Eight Cases of Death Following Injection of Salvarsan, Medical Research Council, Special Report Series, no. 55, London, His Majesty's Stationery Office, 1920.

130 Silbergleit, H., and Fockler. On Icterus and Acute Yellow Atrophy in Syphilitic Patients in Relation to Neosalvarsan Treatment, *Ztschr f klin Med* **88** 333, 1919.

131 Kuznitsky, E., and Fuchs. Ueber Nebenwirkungen verschiedener Salvarsanprparate besonders in Frauen, *Arch f Dermat u Syph* **138** 222, 1922.

132 Masson, L. V. Pathogenie clinique et experimentale des icteres dits arsenobenzoliques, These de Strasbourg, 1925.

133 Thiroux, A., Bouvelet, C., and Arlo, J. Hypertoxicity du novarsenobenzol pour les lapins prepares par injections souscutanees de serum de moutons, *Compt rend Soc de biol* **88** 491, 1923.

At the British military hospital at Cherryhinton an "epidemic" of thirty-seven cases of arsphenamine jaundice occurred, with a mortality of 50 per cent from acute yellow atrophy, although there were no cases of jaundice in the hospital among a large number of patients with gonorrhea. There was a small epidemic of catarrhal jaundice in the same neighborhood at the same time, which chiefly affected school children.<sup>129</sup> With the observations on this "epidemic," those of Todd and Ruge mentioned in the preceding section should be considered.

Stokes, Reudemann and Lemon,<sup>40</sup> of the Mayo Clinic, reported that from 1916 to 1918 they observed only six cases of paratherapeutic icterus, among a similar total number of patients treated with essentially the same technic, type and dose of drug from 1918 to 1920, there were sixty-four cases. They pointed out that during the latter two years there was a series of small epidemics of catarrhal jaundice in the region of Rochester, Minn. In addition, in most of the cases paratherapeutic icterus followed closely an infection of the upper respiratory tract. Nast also stressed the rôle of infections of the upper respiratory tract in predisposing to paratherapeutic icterus. Stokes and his associates mentioned arthritis as a possible factor predisposing to arsphenamine jaundice. One of Severin and Heinrichsdorff's patients and several of our patients complained of arthritis or arthritic pains shortly before the onset of the jaundice.

It seems logical that when two hepatotoxic agents, each in itself insufficient to cause jaundice, affect a particular person they may together bring about the appearance of jaundice. In an epidemic of catarrhal jaundice there must be many latent cases in which the administration of arsphenamine might precipitate frank jaundice. The contributory factor may also be any infection of the respiratory tract or intestinal, arthritic or general infection or toxin that is distinguished by a hepatotropic toxic effect. Renal diseases may also aggravate the susceptibility to hepatic degeneration. Voegtlin<sup>76</sup> noted an increase in the toxicity of arsphenamine to the liver after ligation of the ureters, and Lazerat<sup>134</sup> and Nicaud<sup>122</sup> suggested that functional renal damage may retard the excretion of arsenic and so overload the liver.

Other factors which have been considered as exercising a deleterious effect on the liver and thus predisposing to jaundice are general debility, malnutrition, starvation and perhaps even certain vitamin deficiencies, pregnancy and the puerperium. Kraus,<sup>135</sup> Wolf,<sup>16</sup> Hoppe-Seyler<sup>136</sup>

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134 Lazerat, J. Contribution à l'étude de l'ictère grave apparaissant chez les syphilitiques traités par les arséno-benzènes, Thèse de Paris, 1926.

135 Kraus, F. Ueber Ikterus als "führendes" Symptom, Berl klin Wchnschr 58 725, 1921.

136 Hoppe-Seyler, G. Ueber Lebererkrankungen und ihre Behandlung unter dem Einfluss der Kriegsverhältnisse, Med Klin 15 1105, 1919.

and Gutmann<sup>61</sup> emphasized these factors. It was pointed out that in Holland and Switzerland, where the nutritional effects of the World War were felt least, jaundice was comparatively rare. On the other hand, other observers stated that jaundice was most prevalent after 1918, when nutrition was considerably improved, but one cannot be certain that the effects of years of privation can be remedied in a short time. A number of my cases of paratherapeutic icterus occurred among the Latin-American inhabitants of New York, whose unhygienic environment and improper nutrition are well known.

#### SUMMARY

An investigation has been made of the circumstances associated with the occurrence of jaundice complicating arsphenamine therapy. It was first pointed out that benign and fatal (acute yellow atrophy) jaundice must be considered as the same disease, differing only in severity. Definite anatomic syphilis of the liver (gumma, etc.) is not associated with frank jaundice or with the syndrome of catarrhal jaundice or of acute yellow atrophy.

Before the introduction of arsphenamine frank jaundice in persons with syphilis was rare (an incidence of 0.37 per cent) and occurred only in the secondary stage. This former rarity of jaundice with syphilis was compared with its subsequent frequency in both secondary syphilis and tertiary syphilis following treatment with the arsphenamines. This frequency of incidence is so striking as to permit the conclusion that paratherapeutic icterus is caused by the direct toxic effect of the arsphenamines on the liver.

In favor of this view the following facts were pointed out: 1. Experimentally, arsphenamine damages the liver and its functions, and it is possible to cause jaundice in dogs by giving large doses of the arsphenamines. 2. The incidence of paratherapeutic jaundice increases roughly with the quantity of drug used. 3. Paratherapeutic jaundice is also observed as a complication in cases of nonsyphilitic diseases in which treatment is carried out by means of the arsphenamines. 4. There is an occasional concomitant occurrence of other types of intoxications caused by arsphenamine, such as arsphenamine dermatitis.

Against the theory that paratherapeutic icterus is caused by active syphilis of the liver or represents a Herxheimer reaction are the following observations: 1. The patient is usually receiving active treatment with a specific drug. 2. The Wassermann reaction is often negative. 3. No other concomitant lesions of active syphilis are found. 4. In fatal cases *S. pallida* is not found in the liver.

While in cases of jaundice with true recurrent secondary syphilis the Wassermann reaction is always positive, an exanthema is present and there is a history of insufficient treatment, these phenomena are absent in cases of late icterus, which is therefore not to be regarded as an active syphilitic hepatorecurrence. The objection that the delay between the last injection of arsphenamine and the first appearance of jaundice in cases of late icterus speaks against the arsphenamine etiology of paratherapeutic icterus was met by the following facts: 1. The period of latency is not a haphazard interval but is limited to approximately ten months. 2. Even in the absence of jaundice, the liver and its functions may be damaged during this latent period. 3. Other well known hepatotoxins often show a similar latent period.

It has been demonstrated experimentally that young and regenerating hepatic tissue is relatively insusceptible to hepatotoxins. A liver injured by a certain hepatotoxin and therefore undergoing regeneration can subsequently withstand larger doses of the same toxic substance. Therefore, when arsphenamine is given to a patient suffering from paratherapeutic icterus, it is usually received by a liver which contains regenerating or recently regenerated tissue and which therefore is less susceptible to injury than the original tissue. This fact probably explains the paradoxical cure of arsphenamine jaundice during continued arsphenamine therapy. Attention was also called to the fact that in a small proportion of cases resumption of treatment with arsphenamine causes an aggravation of the jaundice or death from acute yellow atrophy of the liver and that in some cases if treatment with arsphenamine is resumed after the jaundice has disappeared a relapse may take place.

Paratherapeutic icterus cannot be considered identical with epidemic or endemic catarrhal jaundice, it is distinguishable by epidemiological and other evidence.

Finally, attention was drawn to the possibility that certain infections, toxins and other debilitating factors may act on the liver in such manner as to summate with, or potentiate, the effect of the arsphenamine.

#### CONCLUSIONS

Jaundice of the type seen in catarrhal icterus does not occur with definite anatomic syphilis of the liver.

Jaundice occurs in 0.37 per cent of untreated persons with secondary syphilis and is caused by the toxic effect of the generalized spirochetosis.

Since the introduction of arsphenamine, jaundice has been observed with tremendously increased frequency, and it has been noted both in cases of secondary syphilis and in cases of tertiary syphilis.

The arsphenamines are hepatotoxic and are responsible for the syndrome of paratherapeutic icterus. The latent period of late icterus does not militate against this concept.

The apparent greater tolerance for the arsphenamines displayed by syphilitic persons suffering from paratherapeutic icterus is attributed to the greater resistance to hepatic poisons of recently regenerated hepatic tissue.

Paratherapeutic icterus is not identical etiologically with catarrhal jaundice.

The significance of predisposing and contributory factors, such as endemic catarrhal jaundice, malnutrition, etc., has been discussed.

#### ANALYSIS OF CASES

The table contains an analysis of the cases observed in the medical service of the Mount Sinai Hospital during the past five years. The number of cases of tertiary syphilis of the liver and the combined total number of cases of catarrhal jaundice, acute and subacute yellow atrophy and coarse nodular cirrhosis have been included for comparison.

In the cases of late icterus the average length of the period elapsed since the last injection of arsphenamine was almost four months, an average delay much longer than that usually reported in the literature. The shortest interval was two weeks, and the longest eight months.

**CASE 1 *History and Course***—V. L., a retired fruit broker, aged 65, was admitted to the service of Dr. B. S. Oppenheimer on Nov. 6, 1933. His wife had had several miscarriages, however, the patient said that he had not had venereal disease. He was known to have had hypertension for ten years and had been suffering from dyspnea on exertion for the past five years.

Recently, during the course of a routine physical examination the Wassermann reaction of the blood was found to be positive. The patient then received a course of intravenous arsenical antisyphilitic injections, the last injection of which was given two weeks before he was admitted to the hospital. Shortly after the last injection he experienced a chill. Four days after the chill his right wrist became red, hot, swollen and painful, and four days later he vomited several times and became jaundiced.

Physical examination revealed the patient to be decrepit and jaundiced. His pupils reacted normally. The lungs were clear. The heart was enlarged downward and to the left, and there were a systolic and a diastolic murmur at the base. The blood pressure was 185 systolic and 85 diastolic. The right wrist and the right ankle were swollen, red and tender. The neurologic examination gave negative results. The diagnosis was paratherapeutic icterus, syphilitic aortitis and gonorrheal arthritis.

The temperature varied between 101 and 103 F. The white blood cell count was 28,600 per cubic millimeter, 92 per cent of the cells being polymorphonuclears. The van den Bergh reaction in the direct phase was prompt and positive and in the indirect phase showed 2.5 mg of bilirubin per hundred cubic centimeters of serum. The icteric index was 35. The total phase showed that the cholesterol content of the blood was 160 mg per hundred cubic centimeters, and the esterified

fraction was 65 mg. The Wassermann and Kahn reactions of the blood were 4 plus. The urine contained tyrosine and urobilin. The stool was brown at all times. Fluid obtained on aspiration of the right wrist joint revealed gram-negative intracellular diplococci, which proved on culture to be meningococci. The patient was given a diet high in carbohydrates. Specific treatment was not given.

Three days after the patient was admitted he became stuporous. His neck was rigid, and the Kernig sign was elicited. A spinal tap yielded cloudy fluid, containing 2,000 cells per cubic millimeter, of which 70 per cent were polymorphonuclear leukocytes. Meningococci were present in the culture of the fluid. Antimeningococcic serum was administered intraspinally, intramuscularly and intravenously. The patient soon brightened mentally, the fever and swollen joints subsided, the spinal fluid became sterile and the cell count diminished rapidly.

### *The Incidence of Jaundice With Syphilis*

Condition	Total Number of Cases	Deaths
Icterus syphiliticus praecox	4	0
Paratherapeutic icterus with syphilis	24	1 (case 1)
Secondary syphilis	4	
Tertiary syphilis	20	
Total	24	
Early icterus	12	
Late icterus	12	
Total	24	
Paratherapeutic icterus in nonsyphilitic persons	3	0
Early icterus	2	
Late icterus	1	
Total	3	
Total number of cases of jaundice with either syphilis or arsphenamine therapy or both	31	1
Tertiary syphilis of the liver without jaundice (one patient faintly jaundiced)	12	6
Catarrhal jaundice, acute and subacute yellow atrophy and coarse nodular cirrhosis in nonsyphilitic persons	99	14

The patient had been doing well for two weeks and was out of bed when he relapsed into stupor. The spinal fluid at this time was normal. The icteric index was down to 15, and the van den Bergh test in the direct phase gave negative results and in the indirect phase showed 0.2 mg of bilirubin per hundred cubic centimeters. The urine no longer contained tyrosine but still showed urobilin. The cholesterol content of the blood had diminished to 115 mg per hundred cubic centimeters, with only traces of cholesterol esters. The scleras were still slightly jaundiced.

The patient remained in a stupor and died four days after his relapse. The cause of death was clinically unclear.

*Postmortem Examination*—This was carried out on December 6 by Dr. Lichtenstein, Dr. Jarcho and Dr. Bender. The anatomic diagnosis was confluent bronchopneumonia of the lower lobe of the left lung (the cause of death), chronic and acute bronchitis, healing meningococcic meningitis, meningococcic arthritis of the right wrist and right ankle, focal parenchymatous necrosis of the liver, with

atrophy, fibrosis and regeneration, icterus (slight), syphilitic mesaortitis, chronic rheumatic valvulitis of the mitral, aortic and tricuspid valves and acute infectious splenic swelling

**Examination of the Liver** The liver was distinctly smaller than normal, it weighed 1,000 Gm. Its capsule was finely and diffusely wrinkled. The consistency was flabby throughout, the left lobe seeming flabbier and more atrophic than the right lobe. The cut surface was yellowish brown. The normal lobulation was distinctly visible, but the individual lobules were small. The hepatic and portal vessels were grossly normal. The extrahepatic bile ducts and the gallbladder appeared to be normal. The gallbladder contained dark green, viscid bile.

Sections of the liver were stained with hematoxylin and eosin, Van Gieson's stain and sudan III and by the silver impregnation method. The normal lobular

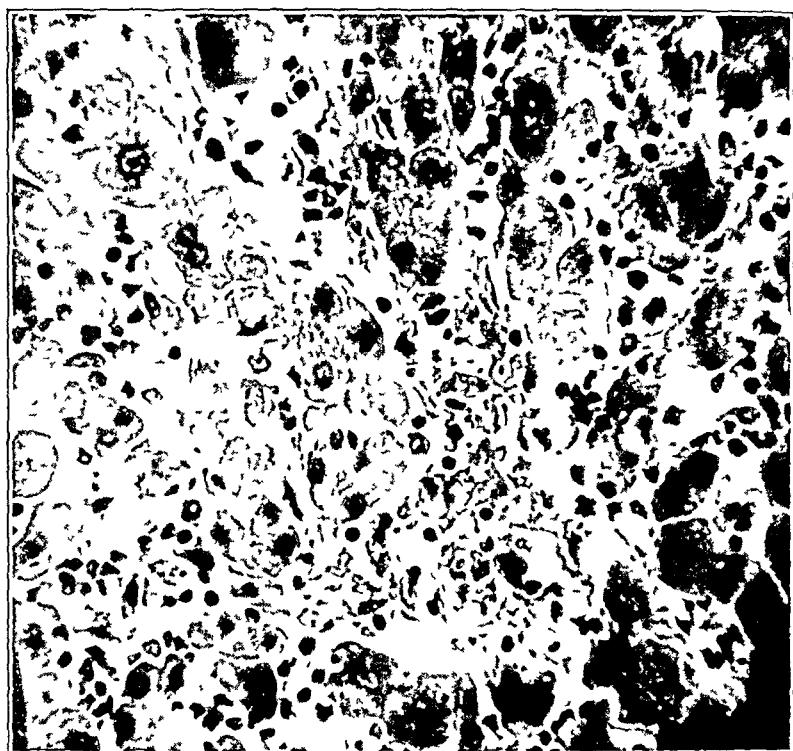


Fig 1—Foci of degeneration of hepatic cells, with an invasion of lymphocytes and polymorphonuclear leukocytes. Hematoxylin and eosin stain.

structure of the liver and the normal appearance of the cords of the liver cells were generally easily recognizable on low power examination in sections made of the right lobe of the liver. In sections of the left lobe the cords were broken up by a dissociation of each cell from its neighbors. Scattered about the liver lobule, but more commonly located in the central zone, were foci varying in size from that of a single cell to one fifth of a lobule, in which the hepatic architecture was not present or was discernible with difficulty. The liver cells were polygonal, with mottled granular cytoplasm and round vesicular nuclei with a single large reddish-blue nucleolus. A moderate degree of fatty vacuolation of the cells in the central areas was noted. Here and there, singly or in groups, as mentioned previously, cells were seen the cytoplasm of which was very granular, stained faintly with eosin and contained much granular green bile pigment. Many of

these cells were shrunken and rounded, sometimes with only an amorphous mass of débris remaining. The nuclei of these cells were faint or absent. In such areas the capillaries were wide and the framework was conspicuous. A few bile thrombi were noted in the bile canaliculi. Occasionally an area of such cells was invaded by lymphocytes and a few polymorphonuclear leukocytes (fig 1). Elsewhere these foci contained a few thickened collagen fibers which stained red with the Van Gieson stain or were entirely replaced by small scars (fig 2). The reticular framework throughout, as revealed by the Van Gieson and the silver stain, was coarse and thickened. In the vicinity of foci of degeneration large cells with copious amounts of cytoplasm containing little or no bile pigment were seen. Their nuclei were large, dark-staining and somewhat irregular and often contained

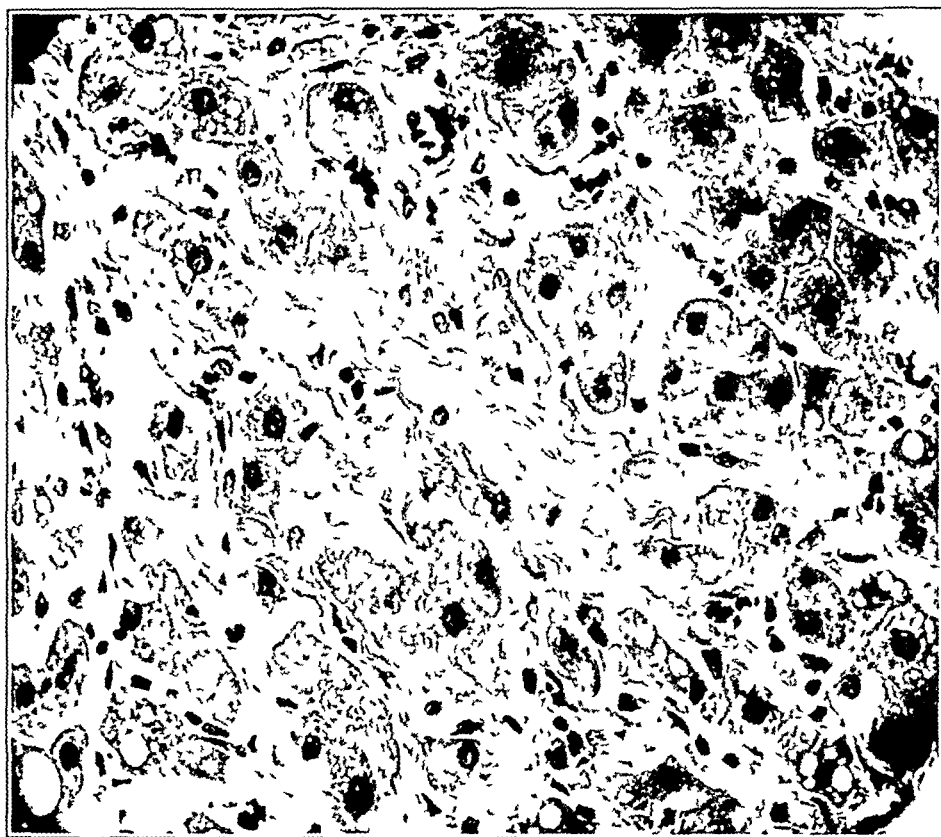


Fig 2—A collagenous scar in the parenchyma of the liver. Hematoxylin and eosin stain.

multiple nucleoli. Cells with multiple nuclei were common, but no mitoses were discovered. A few nuclei contained a large clear vacuole, which pressed the chromatin to the periphery—so-called glycogen degeneration of the nucleus. The Kupffer cells were generally spindle-shaped and sometimes showed small cytoplasmic vacuoles. Some round cells were present in the sinusoids, which in the central zones were moderately congested with red blood cells. Many of the portal spaces were heavily infiltrated with lymphocytes and polymorphonuclear leukocytes, and in some instances the spaces showed proliferation of fibroblasts and thickening of the connective tissue. The portal vessels and bile ducts were without significant change.



This case appears to have been one of paratherapeutic icterus in which the meningococcic infection was possibly a factor contributing to a slight extent toward the degeneration of the liver. However, since jaundice is unknown in cases of meningococcic infection, there can be little doubt that the injections of arsphenamine were of primary importance. Death occurred from confluent bronchopneumonia at a time when the jaundice had almost entirely disappeared and the liver was evidently improving. The opportunity to examine the liver at this stage was very fortunate, since it demonstrated clearly both the focal necrosis of the liver and the processes of healing, i. e., regeneration and scarring. There were no indications of an acute or chronic inflammatory process in the liver.

CASE 2—I L. was a Pole aged 42. His past history was irrelevant. Eight years previously the patient had a chancre. The Wassermann reaction was 4 plus, and treatment was begun with arsphenamine and mercury. The injections of arsphenamine were frequently followed by seizures of mental confusion. Four years later treatment was resumed, with similar reactions. One year before hospitalization the Wassermann reaction was 2 plus, and treatment with neoarsphenamine was started. The reaction was so severe that intravenous therapy had to be abandoned after several injections, and treatment was continued with bismuth.

Seven and a half months after the last intravenous injection the patient complained of weakness and anorexia, and three days later he became frankly jaundiced. He was well nourished and in good general condition. The liver was tender and sharp-edged and was felt 3 cm. beneath the costal margin, the spleen was not palpable. The chest was normal. There was evidence of mild dementia paralytica. The Wassermann reaction was negative, and the Kahn reaction was reported as plus-minus. The hemoglobin content was 98 per cent and the white blood cell count was 6,900 per cubic millimeter, with polymorphonuclear leukocytes, 76 per cent, lymphocytes, 14 per cent, monocytes, 4 per cent and eosinophils, 6 per cent. The stool was always brown and gave a positive reaction for urobilin, as did the urine, which was deeply stained with bile. The urea and sugar contents of the blood were normal. The cholesterol content was total, 250 mg. per hundred cubic centimeters, and the esterified fraction, 125 mg., or 50 per cent of the total (normal). The icteric index was 60, the van den Bergh reaction in the direct phase was delayed and positive and in the indirect phase showed a proportion of 1:20,000, or 5 mg. of bilirubin per hundred cubic centimeters of blood serum. Because of the nonobstructive jaundice and the history of intolerance for arsphenamine, a tentative diagnosis of paratherapeutic icterus was made, and conservative treatment was instituted. However, anorexia and nausea prevented the use of an adequate diet, there was mild fever, the liver became further enlarged and ascites appeared, paracentesis yielded 300 cc. of bile-stained fluid. The icteric index rose to 135, and the van den Bergh reaction in the direct phase was prompt and positive and in the indirect phase showed a proportion of 1:10,000, or 10 mg. of bilirubin. The total cholesterol content was 260 mg., and the esterified fraction, 55 mg., or 20 per cent of the total—an indication of parenchymatous hepatic damage. The patient looked, in general, much worse. An attempt to combat anorexia and nausea with small injections of insulin met with success. Potassium iodide was given by mouth, and a suspension of bismuth subsalicylate in oil was administered intramuscularly. Improvement was gradual but satisfactory. In forty-three days

the patient was discharged, the icterus index was then 21. When examined in the follow-up clinic several months later, the patient was well except for signs of mild dementia paralytica.

One may here remark on the long history of intolerance to arsphenamine, the disappearance of anorexia and nausea following insulin therapy and the suspicion that a specific antisyphilitic effect of the bismuth may have been responsible for the improvement. However, in regard to the latter, it must not be forgotten that this patient had ascites and that bismuth is a diuretic.

CASE 3—C. C., a Puerto Rican woman aged 35, ten years previously had an attack of painless jaundice following intravenous antisyphilitic treatment and recovered. Some time after this attack additional treatment was given without complication. During a recent pregnancy she received injections of arsphenamine until delivery, after this she complained of fatigue and frequently of nausea and vomiting. Four months post partum she noted that she was jaundiced, and four months later she was admitted to the hospital, distinctly undernourished, toxic and deeply icteric. The chest was normal. The liver was enlarged, firm and grossly irregular with a large lappet extending downward almost into the right iliac fossa. The spleen was large and firm. The Wassermann reaction was 3 plus, the Kahn reaction was 3 plus, the hemoglobin content was 35 per cent, and the white blood cell count was 3,000 per cubic millimeter, with polymorphonuclear leukocytes 64 per cent, lymphocytes 33 per cent and eosinophils 3 per cent. The stool was light brown, both the stool and the urine were deeply colored with bile. The icterus index was 135, the van den Bergh reaction in the direct phase was prompt and positive and in the indirect phase showed a proportion of 1 to 40,000, or 25 mg of bilirubin. The cholesterol content was 135 mg per hundred cubic centimeters, and the esterified fraction was 25 mg, or 19 per cent of the total. The sugar and urea content of the blood were normal. Because of the long continued jaundice and the irregular function of the liver the diagnosis was coarse nodular cirrhosis caused by delayed arsphenamine poisoning and favored by the puerperium, anemia and malnutrition. Impending cholemia was feared. Because of vomiting it was impossible to establish the usual regimen. An intravenous drip of a 10 per cent solution of dextrose in distilled water, with sufficient insulin to prevent glycosuria, was therefore begun. Though this patient appeared to be sicker than the one in case 2, bismuth was withheld for reasons of control. Improvement was slow and gradual. The intravenous injection of dextrose was discontinued as soon as peroral feeding could be tolerated. The patient eventually left the hospital free from symptoms, although the liver was still nodular.

This case suggests that the salutary effect, if any, of bismuth in case 2 was mediated not by its specific antisyphilitic power but by its effect on the disordered water metabolism. The suspicion that the strain of pregnancy, anemia and malnutrition were contributory etiologic factors abetting the arsphenamine is very strong.

CASE 4—R. A., a man aged 30, was a painter. Following a dietary indiscretion abdominal pain developed, and the patient vomited frequently. He had high fever and became jaundiced the day before he was admitted to the hospital. He appeared to be severely toxic, dehydrated and worn. The liver was small on percussion and

could not be palpated. The icterus index and the values for the van den Bergh reaction were elevated, and the urea content of the blood rose as high as 120 mg per hundred cubic centimeters. The concentration of urine was high. With general treatment and forcing of fluids, the jaundice disappeared rapidly, the azotemia disappeared a little less quickly. The blood pressure was not elevated, there was no evidence of lead poisoning.

The patient stated that he had had a chancre eleven years previously, which had been adequately treated. The Wassermann test had become negative, and it continued to be so.

This was the only case observed in which by any stretch of imagination the condition might be suspected of being tertiary syphilis and jaundice without recent treatment with arsphenamine. However, since the syphilis had been adequately treated years before, the patient could not be regarded as having active syphilis. The case is rather obviously one of intoxication—gastro-intestinal, hepatic and renal—not related to syphilis. Examination for *Spirochaeta icterohaemorrhagiae* was not performed.

# INFANTILISM AND DIABETES MELLITUS

## A REPORT OF EIGHT CASES

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A group of young patients with the manifestations of diabetes mellitus, sexual infantilism and varying degrees of dwarfism has been observed. These patients not only present a definite syndrome but are of interest in view of the recent advances which have been made in the knowledge of the anterior lobe of the pituitary gland. They demonstrate the occurrence of diabetes mellitus in association with hypofunction of the anterior lobe of the hypophysis in spite of the improbability of such a combination as indicated by experimentation with animals. As the result of pituitary dysfunction, as evidenced by dwarfism or at least by delayed adolescence, diabetic symptoms if present should be mild. In all eight cases the condition has been severe.

The functions of the anterior lobe of the pituitary gland have been summarized by Evans,<sup>1</sup> who ascribed to it growth, gonadotropic, lactogenic, thyrotropic and adrenotropic hormones, in addition to a factor regulating fat metabolism and a diabetogenic hormone controlling carbohydrate metabolism. The relationship between carbohydrate metabolism and the anterior lobe of the pituitary gland has been frequently emphasized. Acromegaly especially in the early or active stage, is associated with glycosuria and hyperglycemia in from 10 to 40 per cent of the cases.<sup>2</sup> On the other hand, cases of hypophyseal dwarfism have been reported in which there were lowered dextrose tolerance and an increased sensitivity to insulin.<sup>3</sup> The experimental evidence in regard to this relationship was summarized and augmented

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1 Evans, H M. Present Position of Our Knowledge of Anterior Pituitary Function, *J A M A* **101** 425 (Aug 5) 1933. Collip, J B. Diabetogenic, Thyrotropic, Adrenotropic and Parathyrotropic Factors of Pituitary, *ibid* **104** 827 (March 9) 1935, 916 (March 16) 1935.

2 John, H J. The Possible Relationship Between Acromegaly and Diabetes, *Arch Int Med* **37** 489 (April) 1926.

3 Lucke, H. Der Kohlehydratstoffwechsel bei Erkrankungen des Hypophysenvorderlappens *Ztschr f klin Med* **122** 23, 1932.

by Barnes and Regan,<sup>4</sup> who showed that hypophysectomy in dogs produces an increased sensitivity to insulin and leads to convulsions due to hypoglycemia during a period of fasting. In dogs in which hypophysectomy and pancreatectomy have been performed the blood sugar level remains approximately normal, and diabetes does not develop as it does in dogs subjected to removal of the pancreas alone. The dextrose tolerance in these animals is somewhat reduced, although large amounts of dextrose can be given by mouth without the appearance of glycosuria. Glycosuria can be produced at will in these dogs, however, by the administration of an extract of the anterior lobe of the pituitary gland, and in five of six normal dogs glycosuria and a decreased sugar tolerance were produced by the same means.

It is well recognized that certain diseases, infections and metabolic disturbances in childhood may prevent normal growth and development and that these conditions must be excluded before a diagnosis of hypophyseal infantilism is made. In the group of cases reported here the diabetes mellitus had either not appeared or was adequately controlled at the age of puberty, and it seems doubtful whether this was the cause of the maldevelopment. Infantilism was manifested in the girls by amenorrhea and complete or partial failure of development of the secondary sex characteristics. The breasts were small and undeveloped, the external genitalia and the uterus were infantile in type, and there was an absence or a very sparse growth of pubic and axillary hair. In the boys the same absence or sparse growth of hair was noted, as well as the infantile type of genitalia. A certain degree of dwarfism was present in all. The physical characteristics consisted of a small but well proportioned skeletal and muscular system, and an absence of or a very slight tendency to obesity, in addition to the sexual infantilism. The mentality was normal, manifestations described are those commonly interpreted as being due to a deficiency of the gonadotropic and growth hormones of the anterior lobe of the pituitary gland.<sup>5</sup> They correspond to the infantile proportionate type of dwarfism<sup>6</sup> in which there is no family history of a similar condition and in which none of the more common etiologic factors of dwarfism, such as achondroplasia, rickets or cretinism, is present. There was no evidence of malnutrition, and in all but two patients the diabetes had been fairly well controlled by an adequate diet for some years, in the two patients

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4 Barnes, B. O., and Regan, J. F. The Relation of the Anterior Pituitary to Carbohydrate Metabolism, *Endocrinology* **17** 522 (Sept-Oct) 1932.

5 Shelton, E. K., Cavanaugh, L. A., and Evans, H. M. Hypophyseal Infantilism. Treatment with Anterior Hypophyseal Extract, *Am J Dis Child* **47** 719 (April) 1934.

6 Barker, L. F. A Case of Hypophyseal Dwarfism, *Endocrinology* **17** 647 (Nov-Dec) 1933.

mentioned the diabetes had developed only recently. A somewhat similar case was reported by Joslin<sup>7</sup>. John<sup>8</sup> reported cases of hypopituitarism in five patients, one of these had diabetes, one had a mild case of diabetes, and three had prediabetic symptoms, but all were obese, and the cases were not comparable to those reported here. Steel<sup>9</sup> reported a case of diabetes mellitus in association with dystrophia adiposa genitalis and diabetes insipidus. Cases similar to those observed by us were reported by Apert<sup>10</sup> and by Gardiner-Hill,<sup>11</sup> both of whom expressed the belief that the infantilism was secondary to the diabetes and reported improvement in growth and sexual development following management of diabetes. Fliederaum<sup>12</sup> also reported two cases and expressed the belief that they were of insulogenic origin. He further stated that insulin is indicated in the treatment of certain cases of infantilism without diabetes.

#### REPORT OF CASES

CASE 1—D. M., a white girl aged 17 years, was admitted to the University Hospitals on Aug. 1, 1933, for management of diabetes. There was a rather indefinite history of polyphagia and polydipsia dating back to 1929. In 1931 the patient began to feel weak and tired, and in March 1932 she consulted a physician, who advised a high caloric diet, on which she gained 8 pounds (3.6 Kg.). There was no glycosuria at that time. Early in the spring of 1933 the patient again began to feel weak and tired and to lose weight. At that time sugar was found in the urine by her physician, and she was placed on a regimen of diet and insulin. There was no family history of diabetes, and all the other members of her family had developed normally.

The patient was well proportioned but poorly nourished and appeared to be about 12 years of age. She was 5 feet, 1 inch (about 154.5 cm.) tall and weighed 80 pounds (about 36.4 Kg.). She had never menstruated. The axillary hair was normal, but the pubic hair was sparse. The breasts and nipples were undeveloped and were of infantile type, and the external genitalia were small and infantile. Otherwise physical examination gave negative results, except that congenital bilateral cataracts were noted.

The Wassermann reaction was negative. The hemoglobin content of the blood was 95 per cent of normal, and the erythrocyte count was 5,110,000. The urine

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7 Joslin, E. P. *The Treatment of Diabetes Mellitus*, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 877 [case 3620].

8 John, H. J. *Hypopituitarism and Diabetes*, *Endocrinology* **9** 397 (Sept.-Oct.) 1925.

9 Steel, R. S. *Diabetes and Dyspituitarism*, *Proc. Staff Meet., Mayo Clin.* **2** 216 (Sept. 14) 1927.

10 Apert, E. *Insulin in Diabetes with Infantilism*, *Bull. et mem. Soc. méd. d'hôp. de Paris* **48** 894 (June 20) 1924.

11 Gardiner-Hill, H. *Dwarfism and Infantilism*, *Practitioner* **125** 97 (July) 1930.

12 Fliederaum, J. *Infantilismus insulogenes*, *Ztschr. f. klin. Med.* **24** 86, 1933.

was normal except for the presence of sugar. The basal metabolic rate was plus 19 per cent. Roentgenograms showed the sella turcica to be small, measuring 9 by 4 mm.

The blood sugar content on admission was 266 mg per hundred cubic centimeters. The patient was given a diet of 70 Gm of protein, 70 Gm of carbohydrate and 175 Gm of fat, with insulin in doses of 22 and 15 units (before breakfast and before supper). The blood sugar content at 9 a m had dropped to 124 mg. She was discharged on Aug 9, 1933, at which time she was receiving insulin in doses of 25 and 15 units (before breakfast and before supper), but some glycosuria persisted. She did not do well at home and was again admitted to the hospital on October 19. Her weight had fallen to 72½ pounds (about 33 Kg). An injection of insulin was given at noon, as the blood sugar values in the afternoon were high, and her condition was controlled fairly well by insulin in doses of 18, 7 and 12 units each day. Injections of the anterior pituitary-like gonadotropic hormone from the urine of pregnant women decreased her carbohydrate tolerance slightly but had no other effect. She was discharged on November 24, the urine was free from sugar, and the last determination of the blood sugar content made before discharge showed 140 mg.

The management of the diabetes in the home was unsatisfactory, and she was admitted to the hospital again on Sept 7, 1934. There were no further development of sex characteristics and no increase in stature. Control of the diabetes was difficult but was attained by insulin in doses of 3 units at 3 a m, 7 units at 6:30 a m, 4 units at noon and 12 units before supper. The urine was then free from sugar, no hypoglycemic reactions occurred and the blood sugar content two hours after meals was about 170 mg. She weighed 40 Kg when she was discharged on October 22.

CASE 2—E. E., a white girl aged 20 years, came to the University Hospitals for the management of diabetes on June 1, 1933. She had suffered from boils and localized infections for three years but had noted polyuria and polydipsia for only the past year. Two weeks prior to admission diabetic acidosis and coma had developed, following which she took 30 units of insulin three times a day. There were no history of any serious illness and no family history of diabetes.

The patient began menstruating at the age of 16 years, but the cycles had been very irregular, with periods of amenorrhea lasting several months. The breasts were small and undeveloped. The uterus was infantile in type and congenitally retroverted. The cervix was small. The axillary and inguinal hair was of normal distribution. She was well proportioned but slender. Her height was 5 feet, 3 inches (160 cm), and she weighed 93½ pounds (42.5 Kg).

The Wassermann reaction was negative. The results of blood counts and determinations of the hemoglobin content were normal. The basal metabolic rate was plus 10 per cent. A roentgenogram of the sella turcica showed its size to be at the upper limit of normal, measuring 12 by 7 mm.

When she was admitted to the hospital the blood sugar content was 337 mg per hundred cubic centimeters (at 2 p m), and there was glycosuria. The patient was given a diet of 60 Gm of protein, 60 Gm of carbohydrate and 150 Gm of fat. She was desugarized on June 3 (the blood sugar content was 165 mg), 17 units of insulin were given before breakfast and 10 units before supper. The blood sugar content was 142 mg on June 6 but was increased with therapy with the anterior pituitary-like gonadotropic hormone from the urine of pregnant women to 167 mg on June 9 and increased to 208 mg on June 13. She was discharged on June 14. She was seen subsequently for the purpose of checking the diabetic

condition, her diet was increased, and the dosage of insulin readjusted. When she was examined on Jan 4, 1934, her weight had increased to 121 pounds (about 55 Kg), and she had been menstruating more frequently, although the flow was still scanty. On Jan 7, 1935, the blood sugar content was 159 mg, but she had not menstruated for a year.

CASE 3—E W, a white girl aged 16 years, was admitted to the University Hospitals for management of diabetes on May 6, 1933. Symptoms of diabetes had appeared three years before, and she had been given a diet and, later, insulin. She managed the diabetes for two years, then discontinued the insulin for financial reasons and after six months more ceased to follow the diet. There had been no previous illness of any consequence. One aunt and a cousin on the maternal side of the family had diabetes.

Although the axillary and pubic hair had appeared at the age of 14 years, the patient had never menstruated, and the secondary sex characteristics were poorly developed. The breasts were small and infantile in type, the pubic hair was scanty, the external genitalia were small, and on rectal examination the uterus was found to be small and anteverted, with the cervix conical in shape. The body was fairly well proportioned, although the hips were straight, the chest short and the abdomen rather long and somewhat obese. The patient was just under 5 feet (about 141 cm) tall and weighed 105 pounds (about 47.7 Kg). Her appearance was that of a girl from 12 to 14 years of age. The physical examination revealed that she was otherwise normal, and her mentality was above average.

The Wassermann reaction was negative. The percentage of hemoglobin and the blood counts were normal. The urine contained sugar on admission. The basal metabolic rate was plus 15 per cent. A roentgenogram of the skull showed a sella turcica of normal size, measuring 10 by 7 mm.

The blood sugar content was 362 mg per hundred cubic centimeters on admission. The patient was given a diet of 70 Gm of protein, 70 Gm of carbohydrate and 175 Gm of fat. Thirty units of insulin before breakfast and 20 units before supper failed to control the glycosuria, and the patient was given insulin in divided doses (beginning May 10) and was desugarized with 10 units of insulin every three hours except at midnight. These doses were reduced progressively to 5 units, given every three hours except at midnight, and on June 27 (after seven weeks) the patient was again given two injections of insulin a day, 30 and 20 units. She was discharged on August 1, with no further improvement in dextrose tolerance, the urine was free from sugar and the last value for the blood sugar determined after a meal was 150 mg. Treatment with estrogenic substances (amniotin and theelin) had failed to induce menstruation. The patient weighed 111 pounds (about 50 Kg) when she was discharged, having gained 6 pounds (2.8 Kg).

CASE 4—E B, a white girl aged 17 years, was admitted to the University Hospitals on March 9, 1933, because of diabetes mellitus and underdevelopment. Symptoms of diabetes had appeared when she was 8 years old, and she was placed on a diabetic diet at that time. After six months she was taken to a clinic, where insulin was prescribed in addition to the diet. She continued this regimen with no recurrence of the diabetic symptoms except occasional glycosuria, and her management in the home seems to have been excellent. The patient had been born at full term, weighing  $6\frac{1}{2}$  pounds (about 3,000 Gm), and she had no serious illness in childhood. The members of her family were of normal size and none had diabetes.

The patient had developed normally until the age of 10 years, when she seemingly stopped growing. On admission she had the appearance of a child of



10 years except for a more mature facial expression. She was intelligent and was attending high school. The mammary glands and nipples were infantile, and the external genitalia were characteristic of prepubescence. There were no axillary or pubic hairs except a few on the labia majora. The labia minora were small, and the uterus was of the infantile type, with an elongated cervix. The patient had never menstruated. She was 4 feet, 8½ inches (143.5 cm) tall and weighed 83½ pounds (about 38 Kg). Physical examination showed that she was otherwise normal. She was normally proportioned.

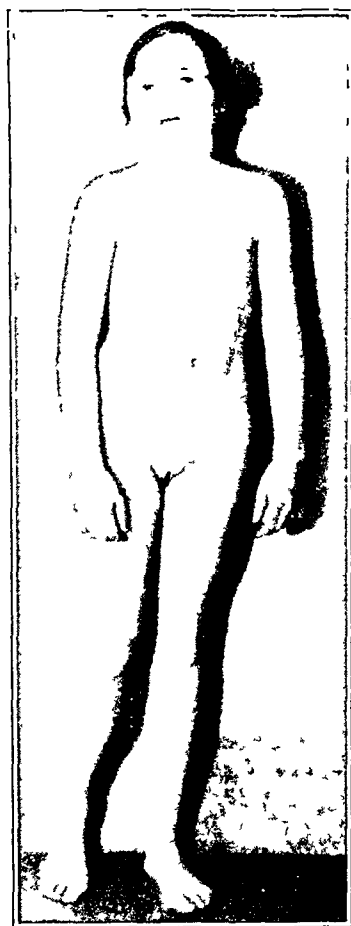


Fig 1—E. B., aged 17 years. The height was 143.5 cm, the weight, 38 Kg. The patient had been diabetic for nine years.

The Wassermann reaction was negative. The hemoglobin content of the blood was 92 per cent of normal, and there were 4,200,000 erythrocytes. The urine was normal except for sugar. Roentgenograms showed a normal sella turcica. There was no evidence of ossification of the epiphyses in the distal ends of the radius and ulnas and the pisiform bones were absent. The visual fields and fundi were normal. The basal metabolic rate was plus 6 per cent.

The blood sugar content was 425 mg per hundred cubic centimeters on the afternoon of March 9, and the urine gave a 4 plus reaction for sugar. The patient was given a diet of 70 Gm of protein, 70 Gm of carbohydrate and 175 Gm of fat, with 30 units of insulin before supper and before breakfast, and the blood sugar value at 9 o'clock the next morning was 316 mg. As the condition proved difficult

to manage, she was given 8 units of insulin every three hours. These doses were reduced to 6 units every three hours, and later the injection at midnight was omitted. The diabetes was controlled by these divided doses. When the patient was again given two injections of insulin daily (40 and 30 units), the blood sugar values were high (253 mg at 9 a m and 131 mg at 2 p m on April 17), and the morning specimens of urine contained a little sugar. She was discharged on April 18, having gained 4 pounds (1.8 Kg). The anterior pituitary-like gonadotropic hormone from the urine of pregnant women, followed by this hormone plus theelin, was given daily during hospitalization, without effect either in establishing the menstrual cycle or on the diabetes.

The patient was recalled to the hospital on July 11, 1934. She had increased in stature and weight (her height was 145 cm and her weight 45.5 Kg), and her breasts were larger and had a consistency which was more suggestive of glandular tissue. There were a few axillary hairs, and a moderate growth of pubic hair had appeared. She had not menstruated. Her general appearance was now that of a 12 to 13 year old girl. The diabetes had been fairly well managed, but she continued to show sugar in the specimens of urine taken after breakfast, and her condition still could not be controlled by two injections of insulin a day. With four injections—5 units at 3 a m, 15 at 6 a m, 17 at noon and 20 before supper—the blood sugar content two hours after breakfast was 147 mg. The urine was free from sugar, and there were no hypoglycemic reactions following the injection of insulin.

CASE 5—L. T., a white boy aged 17 years, was admitted to the University Hospitals on April 13, 1931, because of diabetes which had developed in 1922, when he was 8 years old. He had been given a diabetic diet and insulin (fortunately this was available for clinical use at the time) and had continued on this regimen, although sugar sometimes appeared in the urine. He had developed normally until the age of 10 years, but did not think that he had grown any since. Although he was never able to do hard work, he had had no serious illness. There was no family history of diabetes, and all the members of his family were normally developed.

The patient was underdeveloped and appeared to be about 10 years of age. He was 4 feet, 5 inches (134.6 cm) tall and weighed 56 pounds (25.4 Kg). There was no disproportion in relation to the trunk and extremities, and the skull and chest were of normal contour. The external genital organs were infantile, and there was complete absence of pubic hair. The physical examination revealed that he was otherwise normal except for several carious teeth and a slightly enlarged thyroid gland.

The Wassermann reaction was negative. Blood counts and determinations of the hemoglobin content were normal. Roentgenograms of the skull showed the sella turcica to be of normal size. The basal metabolic rate was minus 11 per cent.

Within the last few weeks before admission to the hospital the patient had become weaker, and the diabetes had become more severe. The sugar content of the blood on admission was 510 mg per hundred cubic centimeters, and the urine gave a 4 plus reaction for sugar. With a diet of 70 Gm of protein, 70 Gm of carbohydrate and 175 Gm of fat, with insulin in doses of 15 and 7 units (before breakfast and before supper), the blood sugar content was 155 mg at 9 a m, but the glycosuria persisted, even when the doses of insulin were increased to 20 and 10 units. When insulin and breakfast were omitted for determination of the basal metabolic rate on April 18, the patient promptly had a severe attack of acidosis, from which he as promptly recovered when he was given 20 units of insulin with

30 Gm of dextrose intravenously. The doses of insulin were increased to 25 and 12 units, with a resultant blood sugar content in the morning of 122 mg, but the glycosuria persisted. Early in the morning of April 22, acidosis again developed, the blood sugar content was 447 mg, and the carbon dioxide-combining power was 10 cc per hundred cubic centimeters of blood. The patient was given his regular dose of 25 units of insulin and later was given 30 units intravenously with dextrose and sodium bicarbonate. He again recovered promptly and was able to eat his regular meal at noon. Better control of the diabetes was attained by giving insulin in divided doses, 5 units being given every three hours. A satis-

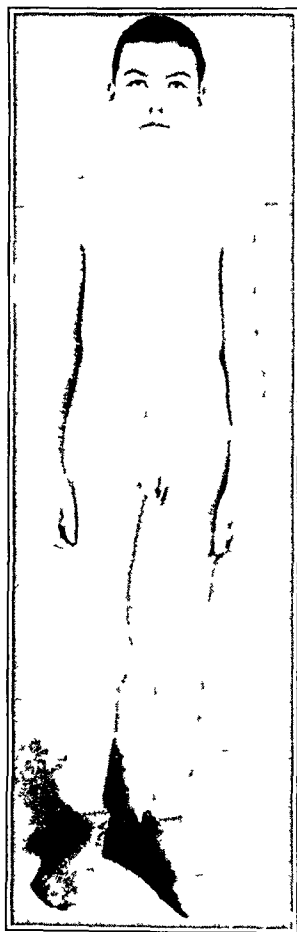


Fig 2—W R, aged 19 years. The height was 155.5 cm, the weight, 36.4 Kg. The patient had been diabetic for seven years.

factory distribution of the doses of insulin was finally achieved, and he was discharged on May 22. At this time he was receiving 5 units of insulin at 3 a. m., 7 units at 6.30 a. m., 5 units at 11.30 a. m. and 17 units before supper. The determinations of the blood sugar content on May 21 were 78 mg. at 2 p. m. and 90 mg. at 7 p. m., and on May 22 the blood sugar content was 90 mg. at 9 a. m.

CASE 6—W R, a white boy aged 19 years, was admitted to the University Hospitals on Feb 21, 1934. Diabetes had developed in his twelfth year. He was placed on a diet and given insulin at the time and had been receiving the same dose of insulin for six years. The urine usually showed some sugar during that time.

He complained of a recurrence of diabetic symptoms recently and had chronic diarrhea for two months preceding his admission. He had been healthy until the age of 12 years, and since then he had had no serious illness except the diabetes, but he had not grown as rapidly or been as strong as other boys. Other members of his family are of normal size, and there is no family history of diabetes.

The patient was undersized, weighing 80 pounds (about 36.4 Kg), and appeared to be about 12 years of age. He was mentally alert, and the proportions of the body were normal. The genitalia were infantile, and there was an absence of pubic hair. The physical examination showed that the patient was otherwise normal except for punctate hemorrhages and exudates in both fundi. The visual fields were normal.

The Wassermann reaction was negative. Blood counts and the percentage of hemoglobin were normal. The protein of the blood plasma content was normal, and determinations of the cholesterol content showed 167 mg per hundred cubic centimeters. Renal function and the urea, the uric acid and the creatinine content of the blood were normal. Urinalysis revealed glycosuria. A biopsy of material from skin and muscle revealed some arteriosclerosis. The basal metabolic rate was plus 10 per cent. Roentgenograms of the sella turcica showed it to be rather small, measuring 9 by 5 mm.

The blood sugar content on admission was 306 mg per hundred cubic centimeters. The patient was given a diet of 70 Gm of protein, 70 Gm of carbohydrate and 175 Gm of fat, and the blood sugar content the next morning (at 9 a. m.) was 473 mg. Injections of insulin in doses of 60, 30 and 50 units each day failed to control the glycosuria, and the blood sugar content on March 2 (at 9 a. m.) was 455 mg. Ten units of insulin given every two hours except at midnight reduced the blood sugar content to 39 mg. As the dextrose tolerance improved, the dose of insulin was rapidly reduced to 3 units, given every two hours, the two injections at 8 and 10 p. m. being omitted. The dose was then increased to 4 units in place of 3, and with this regimen the urine was free from sugar, the blood sugar content was 112 mg at 9 a. m. and 105 mg at 11 p. m. (March 18). Insulin was then again given in three injections daily, in doses of 32, 3 and 20 units, and although the blood sugar values were high in the morning, they were reasonable the rest of the day. The patient was discharged on April 7, having gained 8 pounds (3.6 Kg).

CASE 7—P. W., a white boy aged 18 years, was admitted to the University Hospitals on May 15, 1934, because of diabetes mellitus and a burning sensation of the feet and legs. Diabetes had been recognized in February 1934, with symptoms dating back to the summer of 1933. The patient was given a weighed diet and insulin by his family physician, and he gained in weight and strength for two months. The burning sensation had developed a month prior to his admission, following a cold in the head and intensification of the diabetes. For a short time the burning had involved the thighs and trunk in addition to the feet and legs. Herpes zoster had appeared on the right side of the chest but had disappeared. There were no residual symptoms, although small scars remained.

The patient was 5 feet,  $\frac{3}{4}$  inches (about 154 cm) tall and weighed 93 $\frac{3}{4}$  pounds (42.5 Kg). His voice was high-pitched, and he appeared much younger than 18 years. The pubic hair was sparse, and the genitalia, especially the testicles, were small for his age. Erection of the penis was possible, but he had no desire for companionship of the opposite sex. The remainder of the physical examination revealed that he was essentially normal otherwise. No objective signs of peripheral neuritis could be found.

The Wassermann reaction was negative. The erythrocyte and leukocyte counts and the percentage of hemoglobin were normal. The results of urinalysis were negative except for sugar. The basal metabolic rate was plus 1 per cent. Roentgenograms of the skull outlined a normal sella turcica.

The patient had been taking from 90 to 115 units of insulin a day at home, and on admission to the hospital the blood sugar content was 90 mg per hundred cubic centimeters. Without insulin and on a diet of 70 Gm of protein, 70 Gm of carbohydrate and 175 Gm of fat, the blood sugar content at 9 a m was 349 mg. With insulin in doses of 27, 5 and 15 units daily, the blood sugar values two hours after meals were satisfactory (173, 107 and 129 mg on May 19), but the twenty-four hour specimen of urine gave a 4+ reaction for sugar, and the patient's weight decreased to 89 pounds (40.4 Kg). On May 26, 30 Gm of bread was added to each meal, and on June 2 the patient was given insulin in divided doses, 8 units and, later, 10 units being given every three hours except at midnight. A definite improvement in the diabetic condition resulted, the burning sensation in the feet disappeared, and the patient's weight increased to 92½ pounds (about 42 Kg). He was discharged from the hospital on July 3. At this time he was receiving four injections of insulin daily, in doses of 12 units at 3 a m, 20 units at 6:30 a m, 15 units at noon and 30 units at 5 p m. The urine was free from sugar, and the blood sugar content two hours after breakfast was 90 mg.

CASE 8—D. H., a white boy aged 16 years, was admitted to the University Hospitals on Nov. 4, 1934. A diagnosis of diabetes mellitus had been made two and a half years previously, but he had noted polydipsia and polyuria for a few months before recognition of the disease. The diabetes had been managed by diet and insulin. At the time of admission he was suffering from a recent injury to the left knee.

The boy was well nourished and well proportioned but of small stature. He was 5 feet, 1 inch (about 155 cm) tall and weighed 96 pounds (about 43.6 Kg). The genitalia were small and infantile in type, the pubic hair was scant, and there was no axillary hair. The left knee was stiff and swollen and contained some fluid. The other results of physical examination were negative.

The urine was normal except for the glycosuria, the Wassermann reaction was negative, and the percentage of hemoglobin and the blood counts were normal. The basal metabolic rate was plus 11 per cent. The sella turcica was small (10 by 8 mm), and epiphyseal development was delayed in both wrists.

The blood sugar content was 289 mg per hundred cubic centimeters on admission, and he was given a diet of 70 Gm of protein, 70 Gm of carbohydrate and 175 Gm of fat. Insulin in doses of 30 and 17 units (before breakfast and before supper) failed to desugarize the patient, but doses of 40 and 17 units induced a forenoon hypoglycemic reaction after a blood sugar value of 259 mg had been noted at 9 a m. The blood sugar content at 2 p m was 105 mg. The patient responded satisfactorily to treatment with four injections of insulin daily, in doses of 6 units at 3 a m, 13 units at 6 a m, 5 units at noon and 14 units at supper. The twenty-four hour specimen of urine was free from sugar, the blood sugar content at 9 a m was 152 mg, and there were no symptoms of hypoglycemic shock with this regimen. The condition of the knee cleared up after fluid had been withdrawn on two occasions. The patient was discharged on November 24.

CASE 9—E. B., a white man aged 74 years, was transferred from the surgical to the medical service on June 8, 1934, because of circulatory failure and shock following the induction of anesthesia the previous day for herniorrhaphy. There

were temporary anuria, hyperglycemia (247 mg of sugar per hundred cubic centimeters) and glycosuria. No symptoms of diabetes had been noted previously.

The patient was 4 feet, 10 inches (147.3 cm) tall and weighed 85 pounds (38.6 Kg). He was well proportioned and well developed but was small in all respects. He had weighed 3 pounds (1,306.7 Gm) at birth. All the other members of his family were of normal stature. The axillary and pubic hair was sparse, and the hair on the arms and body was less than normal. There was marked aplasia of the penis and testicles. He had never married. He had had no serious illness.



Fig. 3—D. H., aged 16 years. The height was 155 cm, the weight, 43.6 Kg. The patient had been diabetic for four years.

The basal metabolic rate was minus 4 per cent. Roentgenograms of the skull showed a small sella turcica. Other physical and laboratory findings were unimportant.

The patient was given 5 units of insulin every four hours and dextrose solution and saline solution intravenously until he was able to take a diabetic diet on the fourth day, when the doses of insulin were changed to 10 units before breakfast and 7 units before supper. The blood sugar content dropped to 114 mg. The patient refused to have an operation for his hernia and was discharged on a regimen of insulin, which was taken twice daily in doses of 7 and 5 units, with a restricted carbohydrate diet.

## COMMENT

Of the eight young patients with infantilism who were studied, four were boys and four were girls. The ages ranged from 16 to 20 years. Diabetes developed in one boy and one girl at 8 years, in two boys and one girl at from 12 to 13 years and in one boy and two girls after the age of puberty. All had some degree of proportionate dwarfism. In two patients (girls) the infantilism was partial. All eight had severe diabetes. The two patients with partial infantilism responded to insulin and dietary control as do ordinary adults with diabetes, it was difficult to adjust the distribution of the dose of insulin for the other patients, but five of these were finally given four injections of insulin daily (beginning at 3 a. m.), and satisfactory values for the blood sugar content resulted. Six of the eight patients had received fairly efficient management in the home since the diabetic condition

*Summary of Cases*

Patient	Sex	Age, Years	Infantilism	Height, Cm	Weight, Kg	Basal Metabolic Rate, Per-centage	Sella Turcica, Size in Mm	Onset of Diabetes, Age in Years	Length of Previous Management	Final Doses of Insulin per Day in Units
D M	F	17	Complete	154.5	36.4	+19	9×4	15	2 yr	37.4-12
E E	F	20	Partial	160.0	42.5	+10	12×7	20	2 wk	17.0-10
E W	F	16	Partial	141.0	47.7	+15	10×7	13	2 yr	30.0-20
E B	F	17	Complete	143.5	38.0	+6	10×8	8	9 yr	5-15 17-20
L T	M	17	Complete	134.5	25.6	-11	11×7	8	9 yr	5.7-5.17
W R	M	19	Complete	155.5	36.4	+10	9×5	12	7 yr	32.3-20*
P W	M	18	Complete	154.0	42.5	+1	9×7	17	2 mo	12.20-15-30
D H	M	16	Complete	155.0	43.6	+11	10×8	13	2½ yr	6.13-5.14
E B	M	74	Complete	147.3	38.6	-4	Small	?	None	7.0-5

\* The blood sugar content at 9 a. m. was 253 mg., with glycosuria.

had been recognized, in fact, two patients had received insulin at the time when it first became available for clinical use. Two were seen in this hospital shortly after the diabetes developed. All but one showed ketonuria when having glycosuria, one (E. E.) had a history of recent diabetic coma and in patient L. T. acidosis quickly developed if the morning injections of insulin were omitted and as rapidly disappeared when immediate treatment was given. Two of the four girls while under treatment with sex hormones showed some temporary loss of carbohydrate tolerance. Six of the eight patients had basal metabolic rates of from plus 10 to plus 19 per cent. However, the calories per square meter of body surface per hour may represent the apparent or perhaps the physiologic age rather than the actual age in years. The case of a ninth patient, 74 years old, who had become mildly diabetic, is also reported, there was no previous history of glycosuria.

Roentgenograms either showed that the sella turcica was normal (in four patients) or outlined a sella turcica which was smaller than

normal (in five patients, including the older patient) The largest sella turcica (12 by 7 mm) occurred in one of the patients (E E) with partial infantilism, the next largest (11 by 7 mm) was present in the smallest patient (L T) No deformities were shown

The data are interpreted as indicating that the dwarfism is not the result of the diabetic condition Fliederbaum's<sup>12</sup> idea of an "infantilismus insulogenes" with or without diabetes mellitus which responds to insulin therapy is not confirmed by the data for our patients, since six of eight patients have received insulin treatment for from two to nine years One must bear in mind that the glandular insufficiency may be postponed or latent and that later adolescence is possible If one accepts the idea of a pancreatic hormone produced by the anterior lobe of the pituitary gland (Anselmino and Hoffmann<sup>13</sup>), a deficiency of this hormone, together with failure of production of the gonadotropic and growth hormones, is presented The production of hormone-inhibiting substances (Bachman, Collip and Selye<sup>14</sup>) may be a factor

NOTE.—Six of these patients were reexamined in the summer and fall of 1935 Four had shown definite sexual development and increase in stature D M had not changed at all E E had married, had been pregnant for three months in June 1935 and went to term unevenly E B gained 45 cm in height, axillary and pubic hair were present though scant, she had menstruated once, and her breasts were developed slightly W R showed little change P W had some growth of pubic hair with female distribution D H had darker pubic hair, the genitalia were larger, and his height had increased by 3 cm

#### SUMMARY

The cases of eight patients, four boys and four girls, from 16 to 20 years of age, exhibiting a syndrome of infantilism ranging from the partial to the complete type, apparently due to hypofunction of the anterior lobe of the pituitary gland, with proportionate dwarfism and severe diabetes mellitus, are reported The coexistence of pituitary insufficiency and diabetes mellitus in these patients is not in accord with the results of recent experimental work on the interrelationship of the hypophysis as a whole and the pancreatic islet cells

13 Anselmino, K J, and Hoffmann, F Die pankreatrope Substanz aus dem Hypophysenvorderlappen, über die Darstellung und die Eigenschaften der pankreatropen Substanz, *Klin Wchnschr* **12** 1435 (Sept 16) 1933 Hoffmann, F, and Anselmino, K J Die pankreatrope Substanz aus dem Hypophysenvorderlappen, über die Stoffwechselwirkung der pankreatropen Substanz, *ibid* **12** 1436 (Sept 16) 1933

14 Bachman, C, Collip, J B, and Selye, H Anti-Gonadotropic Substances *Proc Soc Exper Biol & Med* **32** 544 (Dec) 1934



# BENCE-JONES' PROTEINURIA

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The excretion of Bence-Jones' protein occupies a special position in the pathologic picture of the albuminurias. The Bence-Jones body is characterized by precipitation at a relatively low temperature (from 40 to 50 C), followed by clearing of the solution if the heating is continued to 100 C, on cooling the protein appears again.

By far the great majority of cases of Bence-Jones' proteinuria have been observed in association with multiple myeloma of the bone marrow. In a few instances the excretion of Bence-Jones' protein has been noticed in cases of invasion of the bone marrow by some other tumor.

The close association of this peculiar type of proteinuria with disease of the bone marrow gave rise to the question whether this body could be a product of the normal bone marrow. I therefore injected into rabbits an emulsion of cow's marrow, from which the fat had been removed by extraction with ether. Intramuscular or intraperitoneal injection of this emulsion in rabbits was followed by the production of urine which contained a small amount of protein showing the behavior of Bence-Jones' protein.

In the course of further experiments we tried to detect Bence-Jones' protein in the bone marrow itself. The marrow was extracted with ether by careful heating to remove fat. The remaining bone marrow cells were shaken with an equal volume of physiologic solution of sodium chloride and filtered. The clear filtrate showed a precipitate on heating to 60 C, which dissolved somewhat at 100 C and reappeared on cooling. Apparently, some of the Bence-Jones' protein was contaminated with another protein. The latter substance did not redissolve at 100 C, so the fluid did not become quite clear at this temperature. A further difficulty was encountered in the inconsistency of the results on repetition of the experiment.

So far as I am aware, Fleischer,<sup>1</sup> in 1880, was the first who tried to isolate Bence-Jones' protein from the normal bone marrow. Relatively little attention was paid to his communication. Magnus-Levy,<sup>2</sup>

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1 Fleischer, R. *Vuchows Arch f path Anat* **80** 482, 1880.

2 Magnus-Levy, A. *Ztschr f klin Med* **116** 510, 1931, **119** 307, 1932, **120** 313, 1932, **121** 533, 1932.

who in 1932 gave an admirable survey of the literature on multiple myeloma and Bence-Jones' protein, did not mention Fleischer's paper. We have repeated his work but could not reproduce his results. This may well be due to small differences in technic, but for the present we cannot deny that Thannhauser may be right in doubting the value of Fleischer's work.

Ellinger<sup>3</sup> and Askanazy<sup>4</sup> have demonstrated Bence-Jones' protein in the urine, blood and serous exudates in their cases of multiple myeloma. They also succeeded in isolating the protein from the tumors.

Their method was as follows. Emulsions of myelomatous tissue were treated with alcohol, after standing, the precipitate was shaken with distilled water. In the clear filtrate Bence-Jones' protein could be detected.

We applied this method to normal bone marrow. To obtain enough material, we used the bones of young calves, which contained hardly any fat. The marrow was expressed in a press, the resulting marrow juice was treated with two volumes of absolute alcohol and was shaken and allowed to stand for twenty-four hours. The precipitate obtained after filtration or centrifugation was mixed with an equal volume of distilled water and again allowed to stand for twenty-four hours. The resulting filtrate was almost clear and showed only slight opalescence. After the addition of a solution of sodium chloride and acetic acid a precipitate could be obtained by heating the filtrate to a temperature of from 50 to 60 C. The precipitate redissolved almost completely on further heating to 100 C and appeared again on cooling. The reaction was perfectly reversible and could be repeated at will, which furnished the definite proof of the presence of Bence-Jones' protein in the normal bone marrow.

Most of our experiments were carried out with calf's marrow, but in a few cases we have been able to produce the same phenomenon with bone marrow obtained from man. In contrast to the results in our first experiments already described, the demonstration of Bence-Jones' protein could be constantly repeated by following Ellinger's method strictly. This author expressed the belief that after twenty-four hours all the proteins of the marrow are denatured except the Bence-Jones' protein. If the alcohol is allowed to remain in contact with the marrow juice too long, the Bence-Jones' protein is also denatured. This statement could be fully confirmed. After precipitation with alcohol the small amounts of salt present in the bone marrow itself are sufficient to dissolve the Bence-Jones' protein in distilled water.

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3 Ellinger. *Deutsches Arch f klin Med* 62 255, 1899.

4 Askanazy, M. *Verhandl d deutsch Gesellsch f inn Med* 7 32, 1904.

The extract of bone marrow obtained in this way gives the following reactions

1 The clear filtrate begins to flocculate after the addition of salt and acid on heating to 40 C, at 60 C the amount of precipitate is maximal, and at 100 C it redissolves completely. On cooling the precipitate reappears. The protein concentration of the extract is from 3 to 4 per cent.

2 On dialysis of the extract in a Schleicher sack, the protein remains in solution and does not pass through the membrane.

3 The protein is precipitated by dilute nitric acid, sulfuric, hydrochloric, acetic and sulfosalicylic acids and tri-nitrophenol.

4 The addition of two volumes of a saturated solution of ammonium sulfate precipitates the protein completely. The same result occurs on adding an excess of a saturated solution of sodium chloride in an acid medium or on saturating the solution with magnesium sulfate.

5 The biuret, Millon, lead sulfide and xanthoproteic reactions are positive.

The peculiar behavior of Bence-Jones' protein is influenced by variations in the concentration of electrolytes in its solution. This was brought out by the excellent researches of Hopkins and Savory<sup>5</sup> and was confirmed in the Netherlands by Kooyman<sup>6</sup>. Proteins in solution show a positive electric charge on the acid side of the iso-electric point. Adsorbed positive ions increase and negative ions decrease the charge and thereby influence the stability of the protein in suspension. The valence of the ions is of great importance, generally speaking, in a slightly acid solution of Bence-Jones' protein the stabilizing (or dissolving) power of a given salt increases with the valence of its positive ion. Calcium has, therefore, a higher dissolving power for Bence-Jones' protein than sodium. The results of experiments carried out with the extracts of normal bone marrow which we used showed perfect agreement with those which Hopkins and Savory<sup>5</sup> obtained with Bence-Jones' protein in the urine. This may be demonstrated by the following experiment.

The bone marrow extract, as it is obtained, is slightly alkaline and is not precipitated on heating, on addition of acetic acid a precipitate is formed in the cold solution that does not dissolve on heating.

In the same way we found that sodium sulfate has a higher dispersing power than sodium chloride, but less than calcium chloride. Sodium citrate is less active because the citrate ion has a triple valence.

5 Hopkins, E. G., and Savory, H. *J. Physiol.* **42** 189, 1911.

6 Kooyman, J. *Twee gevallen van Bence-Jones'sche albuminurie*, Dissertation, Amsterdam, The Netherlands, 1918.

Urea has a marked promoting influence on the solubility of the protein, but not so strong an influence as that of the electrolytes. The similarity of these results and the facts known about Bence-Jones' protein offer, in my opinion, another proof of the identity of the bone marrow extract and the Bence-Jones body.

Thannhauser and Krauss<sup>7</sup> injected Bence-Jones' protein into rabbits, and the animals showed Bence-Jones' proteinuria. The success of these experiments is largely dependent on the quantity of protein injected, as a minimum of from about 200 to 300 mg seems to be necessary. In a few cases these workers injected chloroform simultaneously to increase the permeability of the kidney cells.

We injected the filtrate of bone marrow into rabbits, this procedure was followed by albuminuria. A part of the protein in the urine showed

*Behavior of Extract of Bone Marrow in Acid Medium*

Solvent	Extract of Bone Marrow, Cc	Water, Cc	Behavior at 60 C	Behavior at 100 C	Behavior on Cooling
Sodium Chloride, Cc					
0.2	2.5	2.3	Coagulum	Coagulum	Coagulum
0.5	2.5	2.0	Coagulum	Clearer	Coagulum
1.0	2.5	1.5	Coagulum	Clear	Coagulum
Calcium Chloride, Cc					
0.025	2.5	2.475	Coagulum	Coagulum	Coagulum
0.050	2.5	2.450	Coagulum	Clearer	Coagulum
0.100	2.5	2.400	Coagulum	Almost clear	Coagulum
0.200	2.5	2.300	Coagulum	Clear	Coagulum
0.300	2.5	2.200	Coagulum	Clear	Coagulum
0.500	2.5	2.000	Clear	Clear	Coagulum
1.000	2.5	1.500	Clear	Clear	Clear

the properties of the Bence-Jones body. In all cases another protein was also present, which made the observation difficult. The most satisfactory method proved to be the close observation of the behavior of the urine on cooling after it had been heated to 100 C.

In addition to its presence in cases of multiple myeloma, Bence-Jones' protein has been found in cases of lymphatic and myeloid leukemia and empyema and in one instance after severe fracture of the knee. In the last instance the phenomenon is easily understood. But why should it occur in empyema and leukemia?

The substrate common to these diseases and multiple myeloma and normal bone marrow is the white corpuscles. This prompted us to investigate these cells for the presence of Bence-Jones' protein. We succeeded in detecting the substance in the pus of abscesses and empyema.

<sup>7</sup> Thannhauser, S. J., and Krauss, E. *Deutsches Arch. f. klin. Med.* **133**: 183 (Aug.) 1920, **137** 257, 1921.

and also in the lymphocytes and other leukocytes in cases of leukemia. The method used was the same as that for finding the protein in the bone marrow, however, even better results were obtained after shaking the pus or the white cells with distilled water, without previous treatment with alcohol. Bence-Jones' protein was also found in the urine of a rabbit that had received injections of an extract of lymphocytes from a patient with lymphatic leukemia.

These experiments make clear why leukemia and the accumulation of pus in the body may give rise to Bence-Jones' proteinuria. The rarity of its occurrence is probably due to a quantitative factor, when the protein is found in cases of leukemia its quantity is usually small. The cause of the excretion of the protein in cases of myxedema remains obscure.

We have examined various organs for the presence of Bence-Jones' protein but could not detect it in the liver, blood plasma, thyroid, kidney and egg white or, strangely, in the spleen. Kooyman stated that he had found the substance in the liver and spleen, but his method is open to criticism. He treated the extract of these organs with a strong acid solution (30 per cent solution of acetic acid) for the detection of the protein body. In this way a precipitate was obtained that dissolved on boiling and reappeared on cooling. In the literature several communications can be found in which sulfosalicylic acid is recommended for the detection of Bence-Jones' protein. In accordance with these directions, we have also used sulfosalicylic and nitric acid, we seemed to obtain excellent results at first, until control experiments showed that in this way Bence-Jones' protein could be detected in any animal protein. If one tests a dilution of urine containing albumin from a patient with nephritis, it is easily possible to duplicate the Bence-Jones reactions by boiling the urine with sulfosalicylic acid.<sup>1</sup> In my opinion, Bence-Jones' protein is not present in the organs as such, as Kooyman stated. Presumably, albumoses are formed by the treatment of protein with strong acids.

Many investigators have wondered at the sometimes enormous quantities of Bence-Jones' protein that can be excreted. They have found it hard to assume that this could all be produced by the myeloma itself. They therefore assumed that the Bence-Jones' protein was derived from the food. It has, however, been shown by Abderhalden and Rostok<sup>8</sup> and in the Netherlands by Hijmans van den Bergh,<sup>9</sup> with the aid of precipitins, that Bence-Jones protein must be an endogenous product, which stands in a close relation to the serum proteins. According to the general opinion, Bence-Jones' protein should be a product of the

8 Abderhalden, E., and Rostok, O. *Ztschr f physiol Chem* **46** 125, 1905

9 Hijmans van den Bergh, A. A. *Ztschr f klin Med* **119** 357, 1932

myelomatous cells The work already described demonstrates that this substance is regularly present in the normal bone marrow, it may even be concluded that the white cells play a special part in its production

#### SUMMARY

The Bence-Jones' protein is found in normal bone marrow, and it is probable that it is a part of the lymphocytes and other leukocytes When bone marrow is broken off (in cases of tumor metastasis) or when the white cells are destroyed (in leukemia and empyema), Bence-Jones' proteinuria does not appear, as a rule, since the quantity of Bence-Jones' protein produced is too small and is, therefore, broken up in the body In cases of multiple myeloma the white cells may have the power to produce a large quantity of Bence-Jones' protein, so much that it cannot all be destroyed and is excreted by the kidneys This is especially true in cases of renal insufficiency

# MODIFYING EFFECT OF VARIOUS INORGANIC SALTS ON THE DIURETIC ACTION OF SALYRGAN

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The use of an inorganic salt in conjunction with an organic mercurial diuretic for the purpose of augmenting diuresis was first reported by Keith, Barrier and Whelan<sup>1</sup> in 1925. These authors showed that a combination of ammonium chloride, administered by mouth, with injections of merbaphen may be effective in causing diuresis in patients with chronic nephritis and edema, when either substance given singly is ineffective. That ammonium chloride and certain other acid-producing salts have a diuretic action when given alone had been noted prior to that time.<sup>2</sup> In recent years the enhancing effect of such acid-producing salts on the diuretic response to mercurial compounds has been repeatedly confirmed. Explanations, however, of the mechanism by which these salts affect the diuretic action of mercury are still at variance.

Keith and Whelan<sup>3</sup> discussed certain effects which are noted when ammonium chloride is administered in conjunction with merbaphen or salyrgan. They stated "One must conclude that an abnormal acid reaction in the tissues need not per se cause diuresis, but since it occurs when the diuretic response is most regular and marked, it must be considered a possible factor in liberating water from the tissues." Jacobs and Keith,<sup>4</sup> in a subsequent report, showed that ammonium nitrate is as effective as ammonium chloride with merbaphen or salyr-

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1 Keith, N M, Barrier, C W, and Whelan, M. The Diuretic Action of Ammonium Chloride and Novasurol in Cases of Nephritis with Edema, *J A M A* **85** 799 (Sept 12) 1925

2 (a) Haldane, J B S. Experiments on the Regulation of the Blood's Alkalinity II, *J Physiol* **55** 265 (Aug) 1921. (b) Gamble, J L, Blackfan, K D, and Hamilton, B. A Study of the Diuretic Action of Acid-Producing Salts, *J Clin Investigation* **1** 359 (April) 1925

3 Keith, N M, and Whelan, M. A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, *J Clin Investigation* **3** 149 (Oct) 1926

4 Jacobs, M F, and Keith, N M. The Use of Diuretics in Cardiac Edema, *M Clin North America* **10** 605 (Nov) 1926

gan, and the suggestion was made that the acid ions play the important rôle in furthering diuresis. In a recent summary dealing with the use of diuretics in various types of edema, Binger and Keith<sup>5</sup> reported on the use of ammonium chloride, calcium chloride and ammonium nitrate with merbaphen or salyrgan. They found that the salts containing chloride produce a greater and more rapid shift in the acid-base equilibrium toward the acid side than do salts containing nitrate, and they gave as their opinion that part of the diuretic effect is probably due to the change in the acid-base equilibrium. Engel and Epstein<sup>6</sup> studied the influence of various inorganic salts on diuresis after the administration of salyrgan. They stated that those substances which produce acidosis, as shown by a fall in the alkali reserve and a rise in the hydrogen ion concentration of the blood plasma, enhance the diuretic action of salyrgan. However, their results were not always consistent. For example, they found that calcium chloride failed to augment the diuresis from salyrgan, yet this salt has been shown by Gamble and his co-workers<sup>7</sup> and by others to produce acidosis. Fliederbaum and Krasucka<sup>8</sup> studied the response to various salts and merbaphen. They observed that the urinary output after the administration of merbaphen is augmented by the peroral administration of ammonium chloride, phosphate, nitrate and bromide, the best diuresis of all occurring with the bromide. Since these investigators found either an unchanged or a diminished response to the administration of merbaphen after the ingestion of urea, calcium chloride, hydrochloric acid, sodium bicarbonate and magnesium oxide, they concluded that the action of the ammonium salts depends on a combination of the effects of the acid anion and the urea-producing ammonium cation.

The administration of sodium chloride was reported by Goldring<sup>9</sup> to increase the effectiveness of merbaphen as a diuretic in two edematous patients with cardiac disease. This he attributed to elevation of a previously subnormal concentration of chlorides in the blood. Elsewhere<sup>10</sup> diuresis occurring after the administration of mercury salts has been considered to be "intimately associated with the available sodium

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5 Binger, M. W., and Keith, N. M. The Effect of Diuretics in Different Types of Edema, *J. A. M. A.* **101** 2009 (Dec. 23) 1933.

6 Engel, K., and Epstein, T. Die Quecksilberdiurese, *Ergebn. d. inn. Med. u. Kinderh.* **40** 187 1931.

7 Gamble, J. L., Ross, G. S., and Tisdall, F. F. Studies of Tetany. I. The Effect of Calcium Chloride Ingestion on the Acid-Base Metabolism of Infants, *Am. J. Dis. Child.* **25** 455 (June) 1923.

8 Fliederbaum, J., and Krasucka, L. Sur l'action diuretique synergetique des composés de mercure et d'ammonium, *Presse méd.* **40** 854 (May 28) 1932.

9 Goldring, W. Edema in Congestive Heart Failure. Effectiveness of Diuretics as a Guide to Prognosis, *Arch. Int. Med.* **44** 465 (Oct.) 1929.

10 Treatment of Cardiac Decompensation, *Queries and Minor Notes*, *J. A. M. A.* **103** 858 (Sept. 15) 1934.



chloride" The ingestion of this salt was recommended in the event of a poor response to salyrgan, especially when there is a lowered concentration of chlorides in the blood The experimental work of Evans<sup>11</sup> on dogs demonstrated a disappearance of the diuretic effects of salyrgan when the animals were rendered hypochloremic, with a reappearance of the response after the administration of sodium chloride All of these observations pertained to patients or animals in a condition of hypochloremia Evans' dogs were also dehydrated because of the loss of fluid and salt incident to a biliary fistula or the vomiting of pyloric stenosis, therefore, the initial failure of diuresis may be attributed as much to lack of available fluid for excretion as to a lack of available chlorides

In contrast to an enhanced diuretic effect, Fliederbaum and Krasucka<sup>8</sup> noted a decreased response to merbaphen after the ingestion of sodium chloride A definite inhibition of mercurial diuresis has been reported after the administration of sodium bicarbonate<sup>12</sup> Engel and Epstein explained this inhibition as due to the production of alkalosis

It is thus apparent that in the studies to which reference has been made there is no unanimity of opinion concerning the mechanism of the increase in mercurial diuresis produced by acidifying salts There is also a paucity of information in the literature regarding the modifying effects of neutral and alkalinizing salts on the diuretic action of mercury The present study was designed to contribute information on this subject which might elucidate some of the points of disagreement Herein are reported the results of a series of controlled experiments carried out at weekly intervals on normal dogs to determine the modifying effect of various acidifying, alkalinizing and neutral salts on the response to the commonly used diuretic salyrgan

#### PROCEDURE

Five normal adult female dogs, weighing between 15 and 22 Kg and in good health, were utilized as the subjects for this investigation The animals were placed on a standard daily regimen as regards the intake of food, water and salt, and in addition they were allowed 30 cc of cod liver oil once weekly Each dog received 35 Gm of boiled horse meat, 30 cc of water and 0.05 Gm of sodium chloride per kilogram of body weight each day The sodium chloride was administered as a 1 per cent solution by stomach tube in the morning The water of the daily ration not consumed during the day was given by gavage at 5 p m

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11 Evans, W A, Jr The Effect of Changes in Salt and Water Metabolism on Salyrgan Diuresis, with Special Reference to the Effect of Permanent Bile Fistula Medical Papers Dedicated to Henry A Christian, Baltimore, Williams & Wilkins Company, 1936, p 204

12 Saxl, P, and Erlsbacher, O Ueber die Verstärkung der Novasurol- (Salyrgan) diurese durch Ammonium Chlorid, Wien klin Wchnschr 42 36 (Jan 10) 1929 Engel and Epstein<sup>6</sup>

No animal was subjected to more than one diuretic test per week. On the day after such an experiment each dog that had been tested was given an additional amount of water and salt (sodium chloride and, if indicated, sodium bicarbonate) to compensate, when necessary, for any excess excreted during the day of diuresis. For the remainder of the weekly interval between tests, the standard daily regimen as outlined was followed. On one or more days preceding each test day, the twenty-four hour volume of urine and the excretion of urinary chlorides were determined. Any marked variation in these figures and any evidence of abnormal thirst or diarrhea was considered sufficient ground for postponing a scheduled test on any dog. Thus, the animals were restored to approximately similar states of water and salt balance for each experiment. On the day of the test the standard daily regimen was suspended until the conclusion of the period of maximal diuresis.

At the beginning of each experiment a specimen of blood (8 cc) was withdrawn from the leg by venipuncture. Neutral potassium oxalate was used to prevent coagulation. The bladder was then emptied by catheterization. Immediately thereafter the calculated amount of the particular salt to be studied, dissolved in 200 cc of water, was administered by stomach tube at a single dose. On the day on which the effect of salyrgan alone was studied, as well as in the study of the effect of water alone, 200 cc of water was given in a similar way without any dissolved salt. In the event of emesis, the vomitus was promptly readministered by tube. Nothing further by mouth was permitted the animal during the next six hours.

The output of urine was determined by catheterization at hourly intervals for five hours. Two hours after the beginning of an experiment salyrgan, when given, was injected intravenously in amounts varying from 0.75 to 1 cc, according to the weight of the animal. Three hours after the first specimen of blood was taken, that is, one hour after the time for the injection of salyrgan, a second specimen of blood was obtained. At the end of six hours the daily ration of food and water less the previously administered 200 cc of water was given. The volume of urine excreted during the twenty-four hour period after the start of the test was determined by catheterization the next morning.

Determinations of the chloride content were carried out on whole blood and on urine after the method of Patterson, as modified by Hald.<sup>13</sup> The carbon dioxide-combining power of the blood plasma was determined by the method of Van Slyke and Cullen.<sup>14</sup> All determinations were made in duplicate.

A total of sixty-seven experiments was carried out as described and may be grouped as follows: (A) Experiments to determine the effect of salyrgan alone. Each of the five animals was tested in this manner. (B) Experiments to determine the effect of salyrgan in conjunction with nine salts: ammonium chloride, calcium chloride, ammonium nitrate, calcium nitrate, potassium chloride, sodium chloride, potassium acetate, potassium bicarbonate and sodium bicarbonate. One acid, phosphoric acid, was also tested with salyrgan. Each of these experiments was performed on four different dogs. (C) Experiments to determine the effect of four salts and of water without salyrgan. The salts studied in this manner were ammonium nitrate, ammonium chloride, sodium chloride and sodium bicarbonate. Each of these experiments was performed on four different dogs.

"Equivalent amounts" of the different salts studied on the test days were given in all cases. The amount of ammonium chloride used was placed arbitrarily at

13 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry Methods*, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 838.

14 Peters and Van Slyke,<sup>13</sup> p. 251.

0.209 Gm per kilogram of body weight, and with this as a basis the amounts of the other substances given were determined by reference to their molecular weights. Thus, the seven salts composed solely of monovalent ions were administered in equimolar doses. Two acid-forming salts (calcium chloride and calcium nitrate) contained a bivalent ion, the equivalent doses of these salts were calculated as one-half the equimolar amount. In the case of phosphoric acid a molar solution was considered to have, after ingestion, 18 times the base-binding capacity of a molar solution of ammonium chloride,<sup>2b</sup> and the dose was computed accordingly.

We were unable to carry out similar experiments with hydrochloric acid, owing to the intractable vomiting which followed its administration in equivalent doses. The use of sulfates was not attempted because the diarrhea which frequently follows their ingestion would interfere with the interpretation of the results.

In order to clarify the procedure followed in each of the experiments, a sample protocol is here given.

Dog 7—A bitch police dog, weight, 21.5 Kg

March 22, 1935, a m, 9 27 First specimen of blood, 8 cc, withdrawn from a vein in the leg and analyzed. Chlorides, 299 mg per hundred cubic centimeters of blood, carbon dioxide-combining power of the plasma, 46.7 volumes per cent.

9 29 Catheterization. Previous twenty-four hour volume of urine, 950 cc, twenty-four hour urinary excretion of chlorides, 1.13 Gm.

9 31 Calcium chloride, 4.65 Gm, dissolved in 200 cc of tap water, administered by stomach tube.

10 31 Catheterization, 28 cc of urine.

11 32 Catheterization, 23 cc of urine.

11 33 Salyrgan, 1 cc, injected intravenously.

p m 12 30 Second specimen of blood, 8 cc. Chloride content of the blood, 326 mg, carbon dioxide-combining power of the plasma, 37.8 volumes per cent.

12 33 Catheterization, 226 cc of urine.

1 31 Catheterization, 236 cc of urine.

2 31 Catheterization, 143 cc of urine. Total volume of urine for the three hour period of diuresis, 605 cc, three hour urinary excretion of chlorides, 4.59 Gm.

3 33 Boiled horse meat, 753 Gm, and water, 445 cc, placed in cage.

March 23, 1935, a m, 9 30 Catheterization. Remainder of twenty-four hour urine, 650 cc, total twenty-four hour volume of urine excreted, 1,306 cc, urinary excretion of chlorides for twenty-four hours 5.284 Gm.

11 00 Boiled horse meat, 753 Gm, water, 645 cc, and sodium chloride, 1.07 Gm given (standard daily ration).

p m The animal given additional sodium chloride, 4 Gm, and water, 1,200 cc, to restore loss on the previous day.

The results of the experiments are set forth in the three accompanying tables. Every figure given is an average of the results for four different animals. The individual results obtained for each dog were in conformity with the averages, except for the several instances mentioned in the text. Therefore, averages are reported for the sake of brevity and simplicity.

The effects of the various salts were determined by comparison with the experiments in which salyrgan alone was given. It was found that when salyrgan was administered the diuresis was most marked during the succeeding three hours, that is, the third, fourth and fifth hours of the test. After that a rapid decline in the urinary output occurred. We therefore selected the volume of urine excreted during this three hour period of maximal diuresis as the basis for comparison, because it best showed the relative diuretic efficacy of the substances. It may be said, however, that in every case the amount of urine excreted in twenty-four hours was found to vary in the same direction as the amount excreted in three hours, though to a less striking degree.

The effects of the various substances on the carbon dioxide-combining power of the plasma and on the concentration of chlorides in the whole blood are reported as the change from the levels at the start of the experiments to those found three hours later. This method of denoting alteration in the blood has been chosen in order to simplify the presentation. The "initial" levels observed at the start of the experiments showed only slight variations from one test day to another, the probable variation<sup>15</sup> in any animal from its average level not exceeding 3 volumes per cent for the carbon dioxide-combining power of the plasma and 6 mg per hundred cubic centimeters for the chloride content of the blood. We found that in our hands the experimental error of the analytic methods employed was of the same degree. In the interpretation of the results, changes in these determinations were not considered significant unless they were in excess of the experimental error.

#### EXPERIMENTS WITH SALYRGAN

The ten substances given with salyrgan may be arranged in three groups according to their effect on the acid-base equilibrium after ingestion and absorption. Accordingly, the presentation of the results of these tests is divided into three sections, dealing with acidifying, alkalinizing and neutral salts.

*1 Acidifying Salts (table 1)*—Phosphoric acid and four acid-forming salts (ammonium chloride, calcium chloride, ammonium nitrate and calcium nitrate) were tested in combination with salyrgan in a series of twenty-one experiments. Without exception there resulted a marked increase in the volume of urine excreted as compared with the tests in which salyrgan alone was used. The average *surplus* in the three-hour volume ranged from 115 cc (58 per cent) with phosphoric acid to 320 cc (193 per cent) with ammonium chloride. Also, in every instance there occurred a significant drop in the carbon dioxide-combining power of the plasma, ranging from an average

<sup>15</sup> Knowlton, A. A. *Physics for College Students. An Introduction to the Study of the Physical Sciences*, New York, McGraw-Hill Book Company, 1928 p. 44

decrease of 8 volumes per cent with calcium nitrate to 15 volumes per cent with ammonium nitrate. The concentration of chlorides in the blood rose definitely in the experiments in which ammonium and calcium chloride were used. With the other acidifying salts and with salyrgan alone, the changes in the chloride content of the blood were slight and not consistent. In addition to the augmentation of the urinary output, a marked increase in the excretion of urinary chlorides for the three-hour period over that obtained when salyrgan alone was given was found in all these experiments. The excretion of chlorides was, of course, greatest in those cases in which a chloride salt was given.

TABLE 1—Average Effect of the Administration of Salyrgan Combined with an Acidifying Salt Compared with the Effect of Salyrgan Alone

Salt Given at Start of Experiment	Dogs Used, No	Volume of Urine for 3 Hours After Administration of Salyrgan, Cc	Surplus of Urinary Volume After Administration of Salt and Salyrgan Over Salyrgan Alone, Cc	Surplus Expressed as Percentage	Change in Carbon Dioxide Combining Power from Initial Level,* Volumes per Cent	Change in Chloride Content of Blood from Initial Level,* Mg per 100 Cc	Urinary Output of Chloride for 3 Hours After Administration of Salyrgan, Gm	Twenty Four Hour Volume of Urine, Cc
None†	4, 5, 6, 7	200			— 1	+ 5	1 443	776
Phosphoric acid	4, 5, 6, 7	315	115	58	—10	+10	1 909	1,017
None†	3, 4, 5, 7	220			— 1	+ 2	1 583	914
Calcium nitrate	3, 4, 5, 7	417	197	90	— 8	— 7	2 683	1,199
None†	3, 4, 5, 6	166			— 1	+ 7	1 251	779
Ammonium nitrate	3, 4, 5, 6	438	272	164	—15	0	2 533	1,122
None†	3, 5, 6, 7	167			— 1	+ 5	1 346	771
Calcium chloride	3, 5, 6, 7	464	297	178	—11	+25	3 726	1,166
None†	3, 4, 5, 6	166			— 1	+ 7	1 251	779
Ammonium chloride	3, 4, 5, 6	436	320	193	—12	+33	3 533	1,073

\* Blood taken at the start of the experiment (initial level) and three hours later (1 hour after the administration of salyrgan)  
† The figures for salyrgan alone differ according to the dogs used

2 Alkalinizing Salts (table 2) —Twelve individual experiments were conducted in which salyrgan and salts of a strong base and a weak acid, namely, sodium bicarbonate, potassium bicarbonate and potassium acetate, were used. In ten of the twelve experiments there resulted a definite decrease in the urinary output as compared with that noted after the administration of salyrgan alone. In the other two experiments (one with potassium bicarbonate and one with potassium acetate) the three-hour volumes of urine were essentially the same as those obtained for the same animals when salyrgan alone was used. However, when the individual results were averaged, there was shown a definite

decrease in the urinary output with each of the three alkalinizing salts. The average *deficit* in the three-hour volumes of urine ranged from 93 cc (47 per cent), when potassium acetate was given, to 103 cc (62 per cent), when sodium bicarbonate was given, as compared with results when salyrgan alone was used. An increase in the carbon dioxide-combining power of the plasma occurred in each case, averaging 5 volumes per cent for sodium bicarbonate, 8 volumes per cent for potassium acetate and 9 volumes per cent for potassium bicarbonate. The concentration of chlorides in the blood was changed only slightly.

TABLE 2—*Average Effect of the Administration of Salyrgan Combined with an Alkalinizing or Neutral Salt Compared with the Effect of Salyrgan Alone*

Salt Given at Start of Experiment	Dogs Used, No	Urinary Output for 3 Hours After Administration of Salyrgan, Cc	Deficit in Urinary Volume After Administration of Salt and Salyrgan Over Salyrgan Alone, Cc	Deficit Expressed as Per centage	Change in Carbon Dioxide-Combining Power from Initial Level,* Volumes per Cent	Change in Chloride Content of Blood from Initial Level,* Mg per 100 Cc	Urinary Output of Chloride for 3 Hours After Administration of Salyrgan, Gm	Twenty Four Hour Volume of Urine, Cc
None†	3, 4, 5, 6	166			— 1	+ 7	1 251	779
Sodium bicarbonate	3, 4, 5, 6	63	103	62	— 5	+ 1	0 112	701
None†	3, 4, 5, 7	220			— 1	+ 2	1 588	914
Potassium bicarbonate	3, 4, 5, 7	105	115	52	+ 9	— 9	0 400	762
None†	4, 5, 6, 7	200			— 1	— 5	1 443	776
Potassium acetate	4, 5, 6, 7	107	93	47	— 8	— 3	0 582	691
None†	3, 4, 5, 6	166			— 1	— 7	1 251	779
Sodium chloride	3, 4, 5, 6	142	24	14	— 2	+21	1 873	689
None†	3, 4, 5, 6	166			— 1	+ 7	1 251	779
Potassium chloride	3, 4, 5, 6	157	9	5	— 4	—19	1 968	719

\* Blood taken at the start of the experiment (initial level) and three hours later (1 hour after the administration of salyrgan)

† The figures for salyrgan alone differ according to the dogs used

and not consistently by the administration of these salts. In every instance in which an alkalinizing salt was administered before the salyrgan the urinary excretion of chlorides for the three-hour period of diuresis was markedly decreased.

3 *Neutral Salts (table 2)*—The neutral salts studied were sodium chloride and potassium chloride. Eight individual tests were performed in which these salts were used with salyrgan. In four of the experiments (two with each salt) the three-hour urinary volume was greater, and in the remaining four smaller, than when salyrgan alone was used. When the figures were averaged, a slight diminution of diuresis was shown when either of the neutral salts was used, but the deficit was

not of significant degree. Measurements of the carbon dioxide-combining power of the plasma showed an average drop of 2 volumes per cent for sodium chloride and of 4 volumes per cent for potassium chloride. Determinations of the chloride content of the blood showed for each salt an average rise of about 20 mg per hundred cubic centimeters. The three-hour urinary excretion of chlorides was markedly increased in each case without any apparent relation to the volume of urine excreted.

#### EXPERIMENTS WITHOUT SALYRGAN

The five substances given without salyrgan were water, sodium bicarbonate, sodium chloride, ammonium nitrate and ammonium chloride. Twenty experiments were performed, each substance being tested on the same four dogs. The results of these experiments are

TABLE 3—*Average Results Obtained After the Administration of Water, Various Salts and Salyrgan Separately\**

Substance Given	Urinary Output for Three Hour Diuretic Period, Cc	Change in Carbon Dioxide Combining Power from Initial Level, Volumes per Cent†	Change in Chloride Content of Blood from Initial Level, Mg per 100 Cc †	Urinary Output of Chloride for Three Hour Diuretic Period, Gm	Twenty Four Hour Volume of Urine, Cc
Water	35	— 1	+ 7	0.016	599
Sodium bicarbonate	45	+11	+ 9	0.042	634
Sodium chloride	54	— 2	+30	0.613	666
Ammonium nitrate	99	—13	0	0.401	743
Ammonium chloride	74	—12	+35	0.653	696
Salyrgan	166	— 1	+ 7	1.251	779

\* Dogs 3, 4, 5 and 6 were used in each of these experiments.

† Blood taken at the start of experiment (initial level) and three hours later.

given in table 3 as averages. The two acidifying salts, ammonium chloride and ammonium nitrate, acting alone provoked a greater urinary output for the three-hour diuretic period than did water, sodium bicarbonate or sodium chloride and thus showed an intrinsic diuretic action of slight degree. The urinary volumes, however, were relatively small compared with those when salyrgan alone was given. With a single exception the changes in the carbon dioxide-combining power of the plasma and in the concentration of chlorides in the blood were the same for any salt, whether it was given alone or in conjunction with salyrgan. This might be expected if one notes the negligible effect of salyrgan alone on these determinations. In the case of the exception (sodium bicarbonate) a greater average rise in the carbon dioxide-combining power and in the chloride content of the blood was observed when this substance was given alone than when it was given with salyrgan. This difference occurred consistently in the individual experiments, but the reason for the discrepancy is not clear.

## COMMENT

The method employed in this investigation was designed to provide a more accurate basis for determining the influence of various salts on the diuretic action of salyrgan than is usually achieved clinically. Most of the previously reported studies on this subject have dealt with clinical experience with patients under conditions that have often been dissimilar. It is our feeling that the method we have used has the following advantages:

- 1 Although edema constitutes the chief therapeutic indication for the use of diuretic drugs, its presence makes the comparative study of diuretic efficacy difficult. The variability of the cause and of the degree of edema is such that the capacity for diuretic response is seldom similar in different patients or in the same patient at different times. In our experiments on normal dogs this factor has been eliminated.

- 2 By replacement of the salt and water lost during a diuretic experiment by a standard daily intake of food, water and sodium chloride for one week, the animals were restored to relatively similar states of salt and water balance. Therefore, all the dogs possessed approximately the same capacity for diuretic response whenever tested.

- 3 In preliminary tests with dogs maintained on a regimen including fluids *ad libitum*, we observed a definite and sustained diuresis from ammonium nitrate alone if this salt was given repeatedly over a period of several days. When salyrgan was injected subsequently there was a poor diuretic response. Therefore, conclusions based on the volume of urine excreted after the injection of one diuretic (salyrgan) after partial dehydration has been produced by a prolonged administration of another diuretic (an acid-producing salt) may be misleading with regard to the true diuretic efficacy of the combination. In this investigation an "equivalent amount" of every salt studied was administered in a single large dose at such a time that its effects would be clearly manifested during the period of action of the salyrgan.

The results of the experiments show that, of the nine salts and one acid given in conjunction with salyrgan, five substances—ammonium chloride, calcium chloride, ammonium nitrate, calcium nitrate and phosphoric acid—caused marked augmentation of diuresis compared with the urinary output after salyrgan alone had been given. That this increase in diuresis was not due to a specific effect of the ammonium ion is shown by the similar results obtained with calcium chloride and calcium nitrate. That the enhanced response was not dependent on the elevation of the chloride content of the blood was demonstrated by the striking increase in the urinary output caused by the two nitrate salts, with no significant alteration in the concentration of chlorides in



the blood The five substances which caused an augmentation of diuresis were all acidifying agents All had one common effect when ingested, namely, the production of acidosis, as shown by a lowering of the carbon dioxide-combining power of the plasma It seems evident, therefore, that the production of acidosis is the factor responsible for the increase in diuresis which occurs when salts of this type are given with salyrgan

The three salts which caused a definite decrease in the response to salyrgan, potassium acetate, potassium bicarbonate and sodium bicarbonate, were all alkalinizing salts This was true of potassium acetate with salyrgan, despite the fact that it is considered as a diuretic when used alone<sup>16</sup> These three salts all had one common effect after ingestion, namely, the production of alkalosis, as shown by an elevation of the carbon dioxide-combining power of the plasma The changes in the chloride content of the blood obtained with these salts were small and not consistent It appears from these observations that the production of alkalosis is the factor responsible for the decrease in diuresis when salts of this type are given with salyrgan

No significant effect on the response to salyrgan was produced by the two neutral salts sodium and potassium chloride The absence of increased diuresis in the presence of a marked elevation of the chloride content of the blood further indicates the lack of influence of the concentration of chlorides in the blood on the extent of diuresis under the conditions employed in these experiments

Chart 1 presents graphically the average effects of the various salts when they were given in conjunction with salyrgan Alterations in the chloride content of the blood and in the carbon dioxide-combining power of the plasma produced by the salts with salyrgan are depicted in the upper portion Corresponding volumes of urine excreted during the three-hour period of maximal diuresis are indicated in the lower part, and for purposes of comparison the average volumes of urine excreted after the administration of salyrgan alone are shown The marked increase in the volumes of urine excreted after the administration of all salts causing acidosis, the absence of any effect on diuresis caused by neutral salts and the definite decrease in the urinary output after the administration of all salts causing alkalosis are apparent No correlation between the extent of diuresis and the changes in the concentration of chloride in the blood can be discerned

Chart 2 presents graphically the comparison between the urinary output resulting when each of four salts was given alone and that resulting from the combined action of each of these salts and salyrgan

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<sup>16</sup> Lyon, D M Observations on Diuretics and Their Uses, Brit M J 2 853 (Nov 11) 1933

The average volumes of urine excreted are depicted for the three-hour diuretic period after the administration of water alone, of the several salts alone, of salyrgan alone and of the salts with salyrgan. The chart illustrates particularly that the diuretic response resulting from the combined action of an acidifying agent and salyrgan is markedly in excess of the sum of the responses obtained with these substances

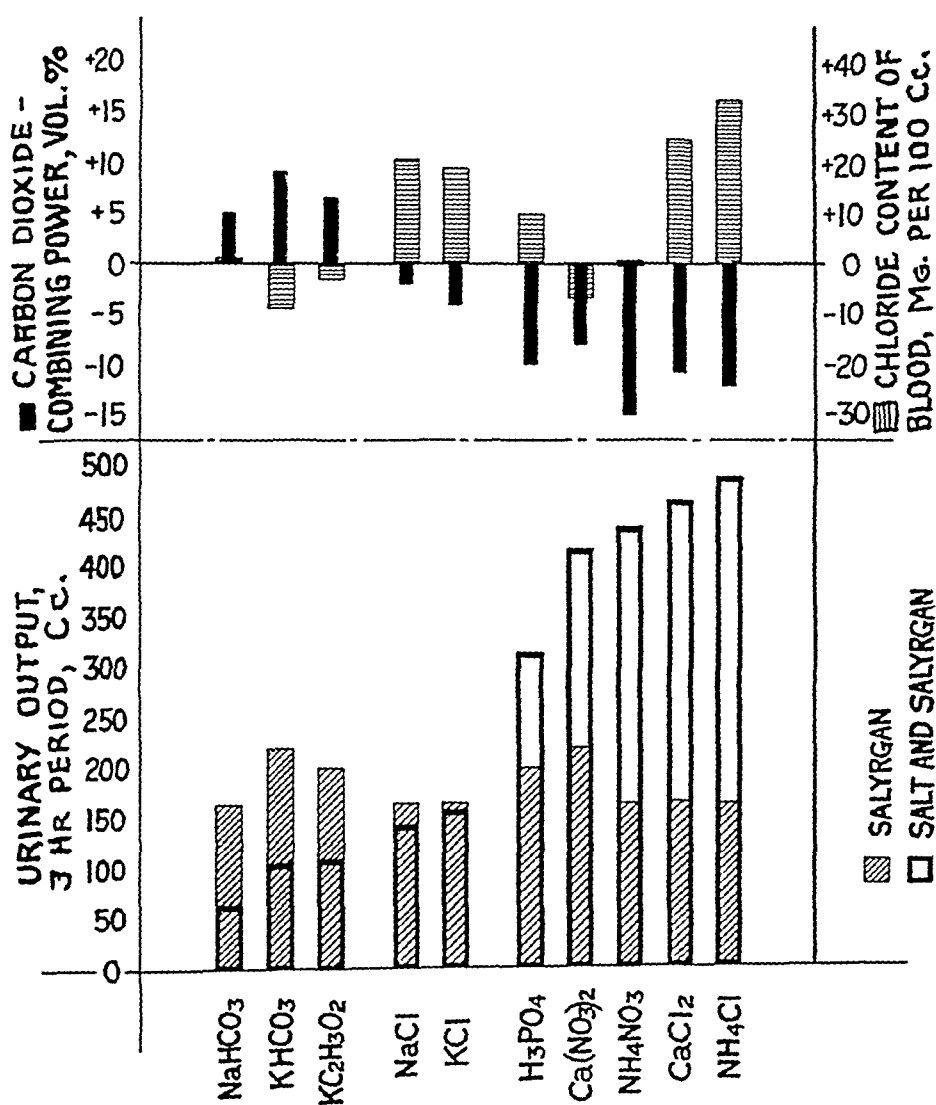


Chart 1—Urinary output and changes in the blood resulting from the combined action of salyrgan and various salts, sodium bicarbonate, potassium bicarbonate, potassium acetate, sodium chloride, potassium chloride, phosphoric acid, calcium nitrate, ammonium nitrate, calcium chloride and ammonium chloride. Each result represents the average for four different animals. The volume of urine excreted after the administration of salyrgan alone differed according to the dogs used. The chart illustrates the correlation between the extent of diuresis and the changes in the carbon dioxide-combining power of the plasma

when given separately. It is therefore apparent that a synergistic diuretic action occurs when one of these acidifying salts and salyrgan

act concurrently. The virtual absence of any modifying effect on the diuresis due to salyrgan when a neutral salt (sodium chloride) is given is also shown. Moreover, it may be observed in this chart that the urinary output after the administration of sodium bicarbonate in conjunction with salyrgan exceeded but slightly the output when this salt alone was used. It is thus indicated that an almost complete inhibition of the diuretic action of salyrgan may occur when an alkalizing salt is given with salyrgan.

Blumgart and his associates<sup>17</sup> stated that the action of ammonium nitrate and salyrgan when given together represented a simple addition of the effects of the two substances. Keith and Whelan<sup>3</sup> suggested that

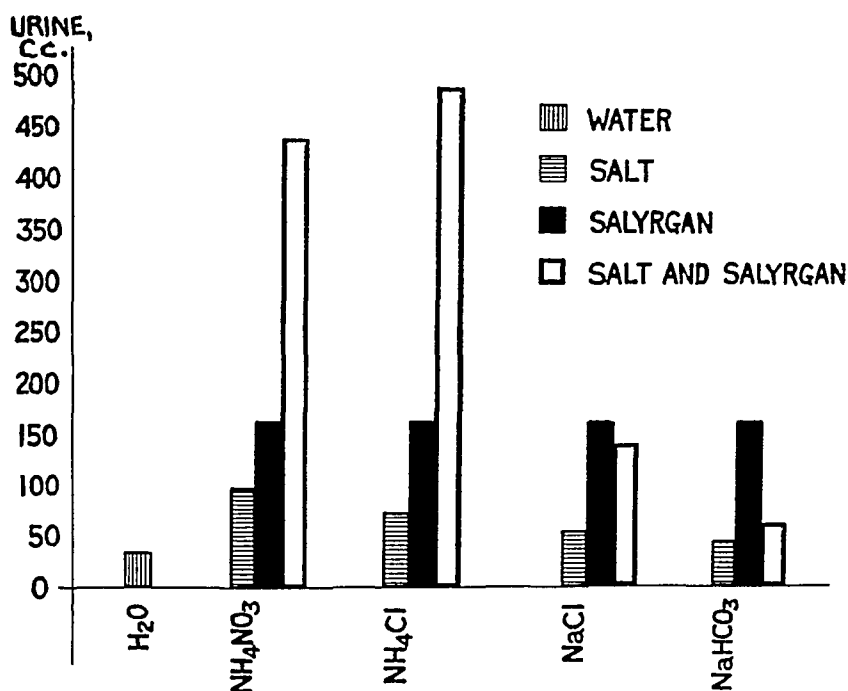


Chart 2—Urinary output resulting from the administration of water alone and of salyrgan and various salts (ammonium nitrate, ammonium chloride, sodium chloride and sodium bicarbonate) given separately and in combination. Each result represents the average volume excreted during a three hour period by the same four animals.

the combined action of ammonium chloride and organic mercurial compounds may be simply cumulative. Our results are not in keeping with these conclusions. On the contrary, they indicate that in normal dogs an acidifying salt and salyrgan acting concurrently have a synergistic diuretic action which gives rise to a urinary output far in excess of the sum of their separate effects.

17 Blumgart, H. L., Gilligan, D. R., Levy, R. C., and Brown, M. G. The Effect of Diuretics on Water and Salt Metabolism, *Tr. A. Am. Physicians* **47**: 304, 1932.

Certain points of clinical interest are brought out by these studies. In the first place, when an acidifying salt is given with salyrgan it should be administered in sufficiently large doses and at such times as to afford the maximal acidifying effect during the time of action of the salyrgan. It is suggested by the work of Dennig, Dill and Talbott<sup>18</sup> that this desired effect is not best obtained by the continuous administration of such a salt. These authors showed that in a person who took large amounts of ammonium chloride daily the degree of acidosis was more marked on the second and third days of administration than subsequently. This occurred even though ingestion of the salt was continued. The single dose method employed in our study is not strictly applicable to the treatment of patients. Most human beings would not tolerate in one dose a quantity of acidifying salt comparable to the amounts given in these experiments. However, it appears advantageous to administer to patients fairly large amounts of an acidifying salt for the two days preceding and on the day of the mercurial injection rather than to give the salt continuously. Such a program was found effective by Saxl and Erlsbacher.<sup>12</sup> We do not wish to imply that all the acidifying agents employed in this study are necessarily of equal value for clinical use. The observations that acidosis is more easily produced, in human beings at least, with ammonium chloride than with ammonium nitrate<sup>19</sup> and that methemoglobinemia occasionally occurs as a toxic manifestation with the nitrate<sup>20</sup> lead us to prefer ammonium chloride for clinical use, in spite of its more disagreeable taste. Again, it seems evident that acidifying salts are distinctly more efficacious than neutral salts, such as sodium chloride, in increasing the diuretic response to salyrgan. In our experiments on dogs which were maintained in a normal state, the administration of sodium chloride caused no significant effect on the diuresis produced by salyrgan. This result does not contradict the observations of others that sodium chloride may be effective in increasing the response to mercurial diuretics in the presence of hypochloremia. The conditions are not comparable in the two cases. However, our findings suggest that even in the presence of hypochloremia a chloride salt which can produce acidosis, such as ammonium chloride, might well be administered in preference to sodium chloride for the purpose of enhancing the diuretic action of salyrgan. Finally, because

18 Dennig, H., Dill, D. B., and Talbott, J. H. Bilanzuntersuchung einer Salmiakazidose, *Arch f exper Path u Pharmacol* **144** 297, 1929

19 Keith, N. M., Whelan, M., and Bannick, E. G. The Action and Excretion of Nitrates, *Arch Int Med* **46** 797 (Nov.) 1930. Binger and Keith.<sup>5</sup>

20 Barker, M. H., and O'Hare, J. P. The Use of Salyrgan in Edema, *J. A. M. A.* **91** 2060 (Dec 29) 1928. Tarr, L. Transient Methemoglobinemia Due to Ammonium Nitrate, *Arch Int Med* **51** 38 (Jan.) 1933

of their inhibiting effect on the response to salyrgan, basic or alkalinizing salts should not be given to patients who are receiving mercurial diuretics

#### SUMMARY

Normal dogs, under controlled conditions, were tested to determine the comparative diuretic responses resulting from the administration of salyrgan alone, of salyrgan in conjunction with various inorganic salts and of several of these salts alone

Four acidifying salts (ammonium chloride, calcium chloride, ammonium nitrate and calcium nitrate) and phosphoric acid when given with salyrgan effected a marked increase in the diuresis as compared with the response obtained from salyrgan alone. A lowering of the carbon dioxide-combining power of the plasma was associated with the enhancement of the diuresis in each case

Three alkalinizing salts (potassium acetate, potassium bicarbonate and sodium bicarbonate) when given with salyrgan produced a definite decrease in the urinary output as compared with that after the administration of salyrgan alone. In each instance a rise in the carbon dioxide-combining power of the plasma was demonstrated

Two neutral salts (sodium and potassium chloride) when given with salyrgan caused no appreciable change in the diuretic response as observed after the administration of salyrgan alone, and the level of the carbon dioxide-combining power of the plasma was not sufficiently altered by their administration

The differences in the response of salyrgan produced by the administration of the various salts showed no apparent relation to coincidental changes in the level of the chloride content of the blood

A synergistic diuretic action was shown to occur when an acidifying salt and salyrgan acted concurrently. The resulting diuresis was far in excess of the sum of the urinary volumes obtained when the acidifying salt and salyrgan were given separately. Conversely, a marked inhibition of the diuretic action of salyrgan was noted when an alkalinizing salt and salyrgan acted at the same time

It is concluded that the modifying effect of various inorganic salts on the diuretic action of salyrgan is dependent on the acidosis or alkalosis which the salts produce on administration

# THE NONSPECIFIC RÔLE OF PRESSOR SUBSTANCES IN THE PLASMA OF HYPERTENSIVE PATIENTS

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The etiology of clinical hypertension is still unknown. Very little has been added to the knowledge of the subject since Janeway's masterly reviews in 1904<sup>1</sup> and 1913<sup>2</sup>. The center of interest has shifted from the rôle of the kidneys to the influence of hyperirritable vasomotor centers, inadequate depressor reflexes (carotid sinuses and aorta), excessive or unbalanced action of chemical pressor substances in the circulating blood, physicochemical changes in the arteriolar media (premature "aging"? )—in short, all the possible physiologic mechanisms involved in the regulation of blood pressure. To complete the circle, the kidneys have again been placed in the foreground by the recent ingenious experiments of Goldblatt and his associates<sup>3</sup>. Their results are particularly significant because for the first time hypertension has been produced in the experimental animal by obstruction of the renal arteries without the necessary association of renal insufficiency.

The difficulty of analyzing the actual nature of the disturbance of the blood pressure-regulating mechanism in hypertensive patients is obvious. For the present one can only speculate on the state of irritability of the vasomotor center or centers or of the carotid sinuses and aortic nerve endings. Emphasis on the hereditary and constitutional aspects of hypertension adds relatively little to the knowledge of the etiology of the condition and rather definitely discourages experimental studies. For these reasons, any attempt to explain certain types of hypertension on the basis of a simple mechanism, objectively demonstrable, warrants serious consideration and careful repetition, even though the underlying assumptions may not be acceptable. Therefore, the present study is the direct result of the publications by Bohn and

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From the Lasker Foundation for Medical Research and the Department of Medicine, the University of Chicago

1 Janeway, T. C. *The Clinical Study of Blood Pressure*, New York, D Appleton & Company, 1904

2 Janeway, T. C. *Nephritic Hypertension. Clinical and Experimental Studies*, *Am J M Sc* **145** 625, 1913

3 Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W. *Studies on Experimental Hypertension. Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia*, *J Exper Med* **59** 347 1934

his associates,<sup>4</sup> who have submitted evidence to substantiate the claim of Volhard<sup>5</sup> that the "pale" forms of hypertension (malignant nephrosclerosis, acute diffuse glomerulonephritis and eclampsia gravidarum) are associated with, and probably the result of, the presence of chemical pressor substances in the blood which are not present in the "red," or benign, types of hypertension

The method of procedure differed in several important particulars from the technic employed by Bohn or by subsequent investigators. Instead of preparing alcoholic extracts of whole blood or plasma, heparinized plasma was used, on the general principle that the less artificial treatment the blood received the more likely it would resemble the circulating blood of the patient. Regardless of the theory of pressor action, i. e., whether it is due to an excess of pressor substance or to a decrease of the normal depressor substances, whole plasma should represent the actual condition in the patient much more accurately than an extract. To surmount the difficulty of dilution of plasma of human blood by the recipient animal's blood volume, the rat was chosen as the test object instead of a larger animal. The importance of controlling the many variables in this type of investigation was clearly recognized from the beginning.

#### METHODS

Venous blood, about 15 cc., was drawn shortly before noon from an antecubital vein of the patient into a syringe containing 1 cc. of a 1 per cent solution of heparin in physiologic solution of sodium chloride. The blood was transferred to a 15 cc. centrifuge tube and centrifugated. The time that elapsed between the drawing of the blood and the injection of the plasma into a rat was usually not more than three and one-half hours.

White rats, weighing about 300 Gm., were used in the experiments. Anesthesia was induced with sodium barbital, given subcutaneously from one and one-half to three hours before the experiment. The dose varied from 5 to 44 mg. but was usually from 10 to 20 mg. The rat was kept warm. A hypodermic needle was introduced into an exposed but unligated vein on the anterior aspect of the thigh, and from 10 to 12 mg. of heparin in 0.5 cc. of saline solution was injected. The needle was left in the vein but was occluded between injections with a stylet passed through a small cork that fitted the hub of the needle snugly. A tuberculin syringe with a capacity of 1 or 2 cc. was attached to the needle for

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4 (a) Bohn, H. Untersuchungen zum Mechanismus des blassen Hochdrucks. Gefassverengernde Stoffe im Blute beim blassen Hochdruck, *Ztschr. f. klin. Med.* **119** 100, 1931. (b) Bohn, H., and Schlapp, W. Untersuchungen zum Mechanismus des blassen Hochdrucks. Weitere Erfahrungen über den Nachweis pressorischer Stoffe im Blute beim blassen Hochdruck, *ibid.* **127** 233, 1934.

5 Volhard, F. Die doppelseitigen hamatogenen Nierenerkrankungen, in von Bergmann, C., and Staehelin, R. *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1931, vol. 6, pt. 1, chap. 4.

each injection. The rate of injection was usually from 1 to 15 cc per minute, and the volume given in a single injection was usually 1 or 2 cc. The interval between injections was usually from five to fifteen minutes.

The blood pressure was recorded from the right common carotid artery by means of a needle cannula connected through an adapter with the rubber tubing of the mercury manometer. The needle cannula was a gage 20 needle cut down to 1 cm, with the point smoothed off and the end surmounted with a bit of solder to keep the ligature from slipping.<sup>6</sup> The solder, however, was later found to be unnecessary, and its absence facilitated the cannulation of the artery without trauma. Physiologic solution of sodium chloride was used in the manometer tubing. The injection of a little of the solution into the lumen of the rubber tube, when the column of blood rose into the small piece of glass tubing near the adapter, was helpful in preventing coagulation and in dislodging small clots in the needle. Gentle squeezing of the rubber tube was also helpful in forcing clots out of the cannula, but serious depressor reflexes at times resulted from these maneuvers. With proper technic, tracings of the blood pressure could be obtained in many experiments over periods as long as two hours.

Artificial respiration, when necessary, was administered through a bent gage 16 needle, 3½ inches (9 cm) long, inserted in the trachea and connected with the compressed air outlet. The rate and depth of respiration were controlled manually.

Each rat was killed at the conclusion of the experiment, and the condition of the heart, lungs and abdominal vascular bed was noted carefully.

## RESULTS

Under the conditions of the procedure just outlined, the rats were only lightly anesthetized during the first hour of the experiment and responded readily to vasomotor stimuli. The mere attachment of the syringe to the needle in the vein of the thigh often initiated a depressor reflex lasting twenty or thirty seconds. A less frequent effect was a pressor reflex. Occasionally the depressor reflex led to a striking fall in the blood pressure and typical vasomotor shock. Intravenous injections of heparinized plasma or other solutions were usually withheld until the reflex changes incidental to manipulation of the needle had subsided. In all instances the figures for rises in blood pressure were calculated from the control level noted just prior to the mechanical reflex, even though the injection was started, in some instances, during the subnormal level of blood pressure of the depressor reflex.

The control blood pressure of this series of 131 rats varied considerably. However, 69 per cent of the initial values fell between 101 and 140 mm of mercury, 20 per cent were above 140 mm, and only 11 per cent were below 101 mm. The largest portion, 40 per cent, had an initial value for blood pressure between 121 and 140 mm. The amount of sodium barbital used for anesthesia did not materially influence the distribution of the control levels of blood pressure within the

<sup>6</sup> Durant, R. R. Improvised Metal Cannula, *J. Lab. & Clin. Med.* **12** 1011. 1927



range employed, although it did seem to affect the rat's response to injected plasma. This feature will be discussed later.

The clinical material represented in these experiments consists of observations on 117 subjects, among which were included persons with various types of hypertension (primary, arteriosclerotic and renal) and a small group of nonhypertensive subjects. Table 1 shows the clinical subdivisions. While the criteria for differentiation of the various groups are somewhat arbitrary, they conform to the prevailing clinical usage. The term "malignant" hypertension is used as the synonym for "pale" hypertension, to include both the primary and the nephritic type, or those cases in which hypertension and its consequences determine the malignant tempo of the disease. Such terminology is admittedly open to serious criticism (as is the whole concept of "malignant" hyperten-

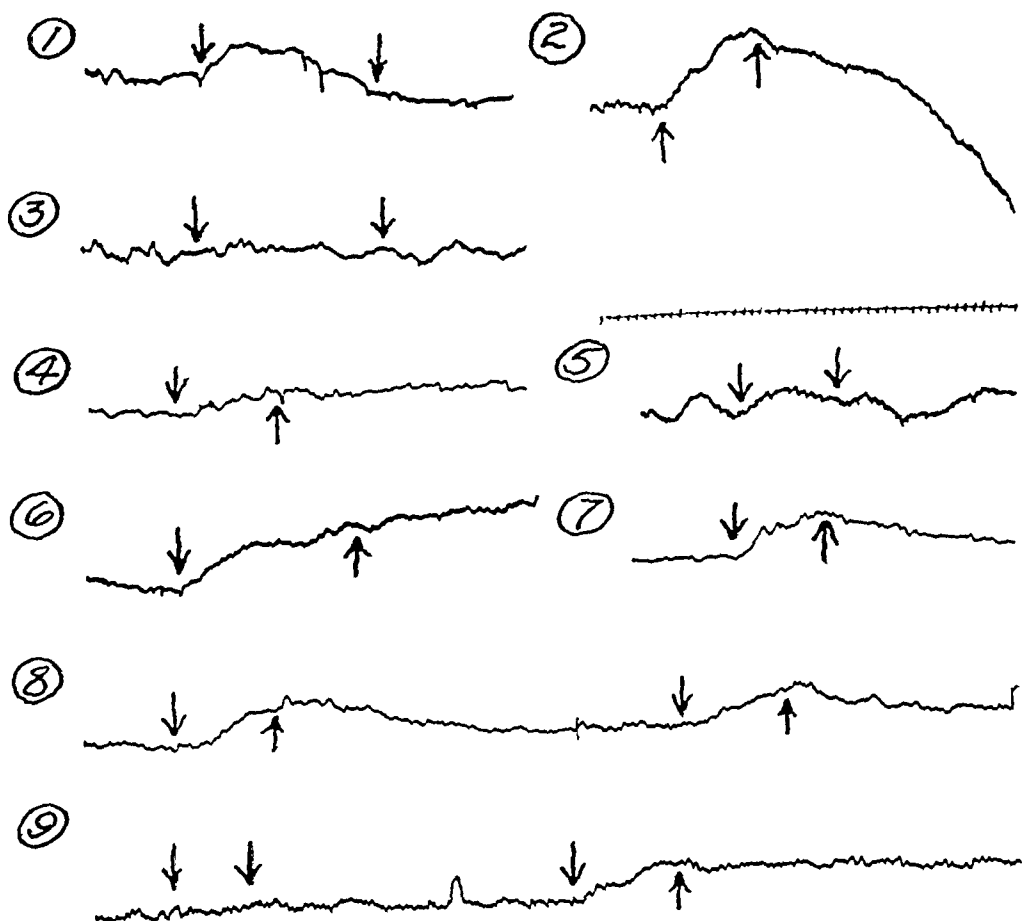
TABLE 1—*Distribution of the Clinical Material and the Plasmas Causing Pressor Effects in the Various Groups*

Diagnosis	Number of Subjects	Plasmas Causing Pressor Effects	
		Number	Percentage
A Primary hypertension			
1 Uncomplicated	26	10	39
2 With myocardial or coronary disease	23	8	35
3 With cerebral vascular disease	12	8	67
Total	61	26	43
B Arteriosclerotic hypertension	13	6	46
C Nephritic hypertension	9	5	56
D "Malignant" hypertension*	17	6	35
E Miscellaneous conditions, nonhypertensive	17	8	47
Grand total	117	51	44

\* This group includes subjects with both primary and nephritic hypertension.

sion), but it is valid for the purposes of this investigation, since Bohn has found pressor substances most constantly in the plasma of these patients.

The general effect on the rat's blood pressure of the intravenous injection of heparinized human plasma was variable, but in only 5 animals was there a "toxic" result in the form of immediate cardiac or vasomotor depression, which occurred with each injection. In all of these rats the blood pressure began to fall during the injection, an occurrence not observed in other rats except as a rare manifestation of a markedly increased blood volume after repeated injections. Apart from these 5 rats, all the others tolerated the single injection of 1 or 2 cc of plasma, and often repeated injections, without untoward effects, provided that respiration was adequate. The immediate response of the blood pressure varied from no change to a definite rise of 6 mm of mercury or more during the injection, followed by a return to the control level within a minute or two. In many instances there was an



- Fig 1—1 (MD, rat 113) Control B P, 114 mm, 8 mm rise from 2 cc of plasma injected in ninety-eight seconds
- 2 (MD, rat 62) Control B P, 100 mm, 15 mm rise from 1 cc of plasma injected in fifty-three seconds Note the late toxic effect
- 3 (MH, rat 101) Control B P, 132 mm, no effect from 2 cc of plasma injected in one hundred seconds
- 4 (MH, rat 76) Control B P, 130 mm, 4 mm rise (?) from 1 cc of plasma injected in sixty-eight seconds
- 5 (MH, rat 26) Control B P, 98 mm, no effect from 2 cc of plasma injected in forty-two seconds
- 6 (UH, rat 106) Control B P, 135 mm, "sustained" 14 mm rise from 2 cc of plasma injected in one hundred and fifteen seconds
- 7 (HC, rat 61) Control B P, 114 mm, 8 mm rise from 1 cc of plasma injected in forty-five seconds
- 8 (HH, rat 69) Control B P, 111 mm, 11 mm rise from 1 cc of saline solution injected in fifty-seven seconds Eleven minutes later the control B P was 115 mm, 8 mm rise from 1 cc of plasma injected in sixty-four seconds
- 9 (HC, rat 161) Control B P, 120 mm, no effect from 1 cc of saline solution injected in fifty-seven seconds Five minutes later the control B P was 120 mm, "sustained" 9 mm rise from 1 cc of plasma injected in fifty-five seconds

In the legends for figures 1 and 2 the abbreviations MD, MH, UH, HC, HH, and NH have the diagnostic meaning indicated in the footnote to table 2 The tracings read from left to right The arrows indicate the beginning and the end of an injection The term plasma denotes heparinized plasma B P denotes blood pressure

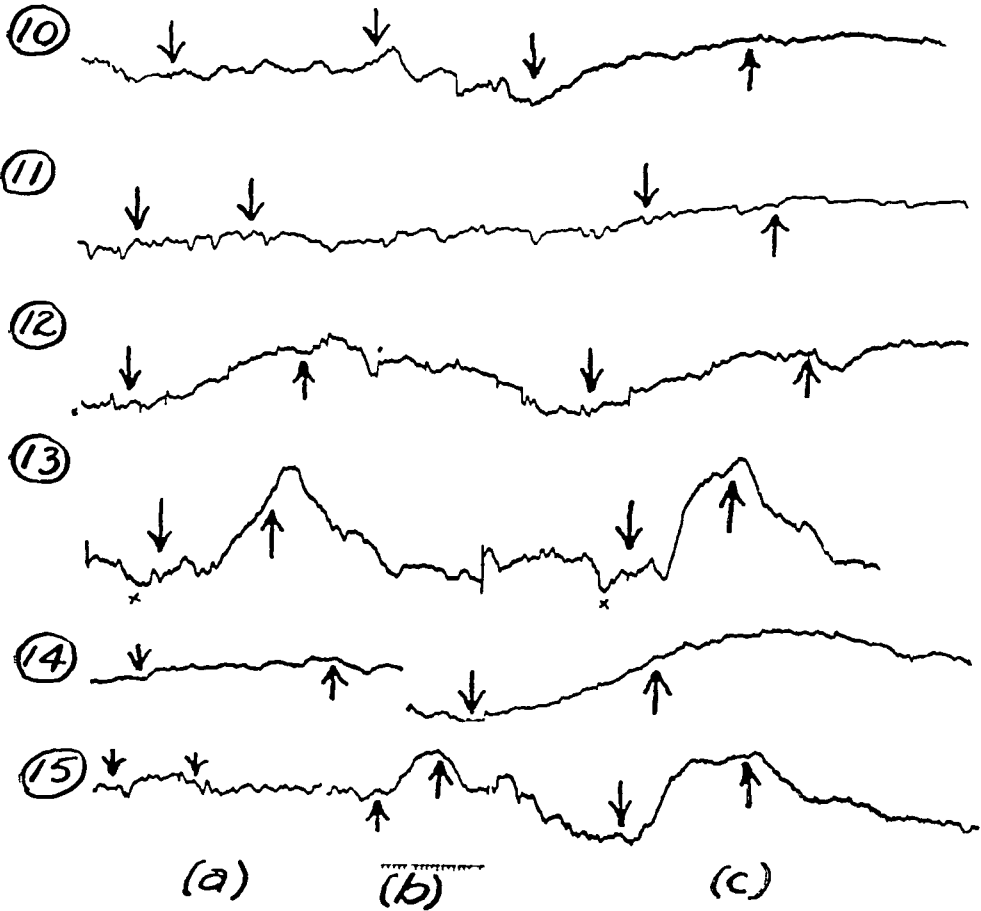


Figure 2

## EXPLANATION OF FIGURE 2

- Fig 2—10 (HC, rat 142) Control B P, 128 mm, no effect from 2 cc of saline solution injected in one hundred and thirty-two seconds Ten minutes later the control B P was 131 mm, "sustained" 15 mm rise from 2 cc of plasma injected in one hundred and thirty-five seconds
- 11 (MH and MD, rat 167) Control B P, 112 mm, no effect from 1 cc of MH plasma injected in seventy seconds Five minutes later the control B P was 112 mm, "sustained" 8 mm rise from 1 cc of MD plasma injected in seventy seconds
- 12 (MH, rat 117) Control B P, 104 mm, 12 mm rise from 2 cc of saline solution injected in one hundred and ten seconds Eighteen minutes later the control B P was 104 mm, "sustained" 15 mm rise from 2 cc of plasma injected in one hundred and fifteen seconds
- 13 (NH, rat 86) Control B P, 146 mm, 21 mm rise from 1 cc of epinephrine (0.0005 mg) in plasma injected in seventy seconds Nine minutes later the control B P was 145 mm, 23 mm rise from 1 cc of epinephrine in saline solution injected in eighty seconds
- 14 (MH, rat 134) Control B P, 132 mm, 4 mm rise (?) from 2 cc of plasma injected in one hundred and twenty-five seconds Twenty-one minutes later the control B P was 72 mm, 16 mm rise from 2 cc of plasma injected in one hundred and thirty seconds
- 15 a and b (NH, rat 53) Control B P, 126 mm, no effect from 1 cc of plasma injected in fifty-eight seconds Thirty-three minutes later the control B P was 80 mm, 9 mm rise from 1 cc of plasma injected in fifty-four seconds c (NH, rat 50) Control B P, 64 mm, 19 mm rise from 2 cc of plasma injected in one hundred and two seconds At 131 mm (not illustrated) a "sustained" rise of 8 mm occurred

TABLE 2—Typical Experimental Results in Relation to the Clinical Diagnosis and the Reactivity of the Rat

Patient	Age	Diagnosis*	Rat	Plasmat			Saline Solution†			Epinephrine in Saline Solution†			Epinephrine in Plasmat			Comment
				Control Blood Pressure, Mm Hg	Pressor Effect	Control Blood Pressure, Mm Hg	Control Blood Pressure, Mm Hg	Pressor Effect	Control Blood Pressure, Mm Hg	Pressor Effect	Control Blood Pressure, Mm Hg	Pressor Effect	Control Blood Pressure, Mm Hg	Pressor Effect	Control Blood Pressure, Mm Hg	
M R	52	UH	34A	131	0(2)		126		126	21(0.5, 1M)	97		97	20(1.2M)		Both carotids ligated
A S	58	UH	47	149	0(1)				121	7(1.4M)	120		120	9(1.4M)		Saline solution injected first
L W	19	UH	64	122	0(1)				110	10(2.4M)	153		153	11(2.4M)		Saline solution injected first
H R	47	UH	95	154	11(2)	18(2.8)	146	4(2)	138	10(2.4M)	139		139	12(2.4M)		Saline solution injected first
I S	33	UH	106	135	14(2.8)				129	11(0.5, 2M)	131		131	9(1.4M)		
J A	49	HH	45	133	0(1)		134	10(1)	132	13(1.2M)	135		135	13(1.2M)		Plasma injected first
H D	58	HH	87	130	12(1)	6(2.8)	112	6(2.8)	90	20(1.2M)	108		108	11(1.2M)		Saline solution injected first
M S	52	HH	120	121	0(2)	11(2.8)	68	11(2.8)								Saline solution injected first
J D	48	HH	151	90	8(2)		141	0(2)								Saline solution injected first
A T	63	HH	153	138	0(1)											
A S	47	HC	35	126	4(2)		116	0(1)								Plasma injected first
H A	58	HC	61	114	8(1)	14(2.8)	142	14(2.8)	143	6(1.2M)	146		146	14(2.4M)		Saline solution injected first
F C	65	HC	90	178	18(2.8)		129	0(2)					127	9(2.4M)		Plasma injected first
D B	54	HO	131	160	10(2)		121	4(1)	122	11(1.2M)	122		122	13(1.2M)		Saline solution injected first
M S	62	AH	88	126	8(1)		131	6(2)	116		116		116	8(2.4M)		Saline solution injected first
E N	73	AH	119	112	10(2.8)		123	0(2)	106		106		106	6(2.4M)		Saline solution injected first
W S	78	AH	128	120	0(2)		136	0(1)								Saline solution injected first
H D	62	AH	157	130	0(2)											
F R	41	NH	21	190	0(2)		126	7(1.8)	110	6(1.4M)	108		108	34(2.1M)		Saline solution injected first
R S	26	NH	65	126	12(1)		148	0(1)	114	20(1.2M)	121		121	8(1.4M)		Plasma injected first
L B	51	NH	85	140	6(1.8)		130	20(2.8)	138		148		148	21(1.2M)		Saline solution injected first
G S	28	NH	132	155	11(2)		140	0(1)	138	18(1.2M)	132		132	8(2.4M)		Saline solution injected first
G S	30	NH	166	148	7(1)		130	0(1)								Plasma injected first
L P	22	MH	41	138	0(1)		138	0(1)	130	14(1.2M)	86		86	23(2.2M)		Plasma injected first
C B	46	MH	57	111	9(1)		104	0(1)	99	14(1.2M)	126		126	14(1.2M)		Saline solution injected first
N D	43	MH	76	130	4(1)		112	6(2)	111	9(1.8)						Plasma injected first
R G	32	MH	153	109	11(2)		108	0(1)	156	0(1)	139		139	15(1.2M)		Saline solution injected first
O D	41	MH	167	114	0(2)		111		142	0(1)						Saline solution injected first
D S	30	MD	39	120	3(2)		156	7(2)								
A L	46	MD	62	100	15(1)		142	0(1)								
F H	43	MD	113	114	8(2)											
J H	41	MD	160	156	7(2)											
J W	52	ND	161	142	0(1)											

\* In this and the following tables UH stands for uncomplicated primary hypertension, HH, for primary hypertension with myocardial or coronary disease, HC, for primary hypertension with cerebral vascular disease, AH, for arteriosclerotic hypertension, NH, for nephritic hypertension, MH, for malignant hypertension, and MD, for miscellaneous nonhypertensive disease.

† In this and the following tables numerals in parenthesis indicate the number of cubic centimeters injected. The letter S stands for sustained effect.

‡ In this and the following tables the first numeral in parenthesis indicates the number of cubic centimeters injected. The second numeral and the letter M give the dilution in terms of millions e. g., '10(2.4M)' indicates a rise in blood pressure of 10 mm of mercury after the injection of 2 cc of a 1 to 4,000,000 solution of epinephrine.

immediate rise of only from 2 to 5 mm, which was interpreted as a doubtful or negative result. Instead of a quick return to the control level, the blood pressure might remain elevated from five to ten minutes or indefinitely. This reaction has been termed "sustained" and was at times definitely attributable to the vasomotor stimulation of respiratory embarrassment following the injection. It was frequently observed, however, apart from dyspnea and was particularly likely to occur when the initial blood pressure was relatively low. This aspect will be discussed later, in connection with the influence of the intravenous injection of saline solution under similar conditions. The different types of reaction of the blood pressure are illustrated in figures 1 and 2.

TABLE 3—*The Association of Low Blood Pressure in the Rat and the Pressor Effect of Human Plasma\**

Patient	Age	Diagnosis	Rat	Plasma			
				Control Blood Pressure, Mm Hg	Pressor Effect	Control Blood Pressure, Mm Hg	Pressor Effect
P S	59	AH	46	138	0(1)	62	16(1)
R S	26	NH	50	131	8(1,S)	64	19(2)
H W	31	MH	51	118	0(1)	62	7(1)
E B	51	NH	53	126	0(1)	80	9(1)
K K	59	UH	66	122	0(1)	70	9(1)
M S	52	HH	103	136	0(2)	76	20(2,S)
E H	43	HH	133	142	5(2)	76	24(1.5,S)
H P	23	MH	134	132	4(2)	72	16(2)
K M	72	HH	125	110	0(2)	96	5(1.8)
G S	37	HC	140	128	0(2)	83	9(1)
J F	79	MD	155	78	20(2,S)	101	5(1,S)
A F	63	HH	158	133	0(1)	87	11(1.2,S)
G C	46	NH	164	140	0(1)	105	19(2)
M S	58	NH	165	142	0(2)	63	12(2)

\* Explanation of the symbols used is given in the footnotes to table 2

The relation between the effects of human plasma on the blood pressure of the rat and the type of clinical material is summarized in table 1. The details of representative experiments are given in table 2. It is demonstrated that definite pressor effects were obtained with the plasmas of from 35 to 56 per cent of the patients in each of the main clinical groups, whether hypertensive or not. Although the number of persons with "malignant" hypertension and of those without hypertension was rather small, the occurrence of negative effects with two thirds of the plasmas of the former and of positive effects with half of the plasmas of the latter is undoubtedly significant. Analysis of the 23 experiments carried out with plasmas from patients with "malignant" or "pale" hypertension indicates clearly that when positive, or pressor, effects were observed, the rise in blood pressure was not greater than that in animals giving a pressor response to plasmas from patients with "benign" hypertension or without hypertension. Thus with plasmas

from the group with "malignant" hypertension, the rise in blood pressure varied between 7 and 15 mm, averaging 9.5 mm, with plasmas from the group without hypertension the rise varied between 5 and 15 mm, averaging 8.2 mm. There was no qualitative difference between the effects of plasmas from patients with "malignant" hypertension and those of plasmas from other patients.

The influence of many variables is possible in experiments of this type. To mention only the more obvious ones, there are the level

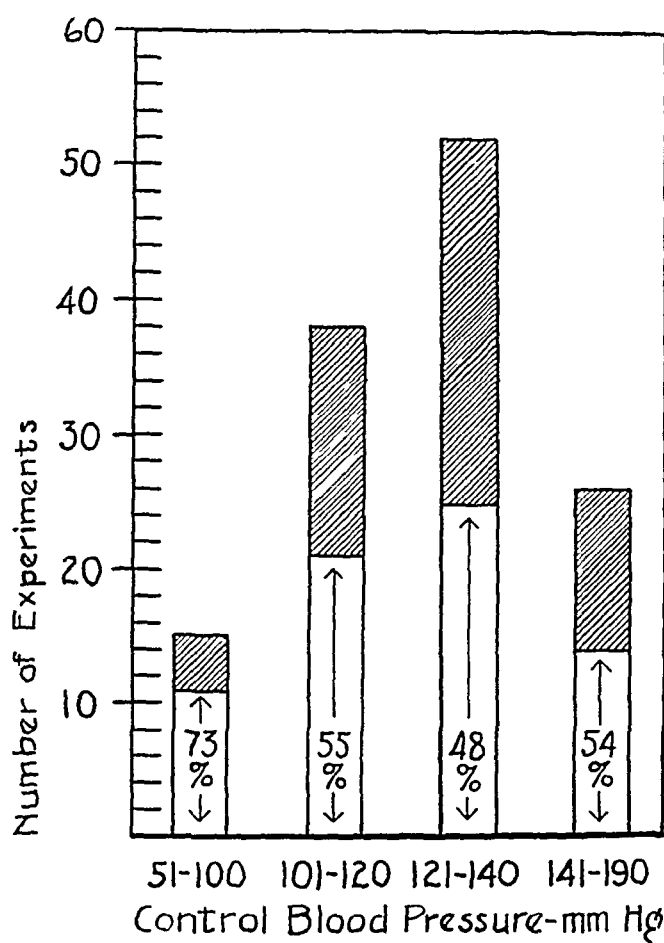


Fig 3—The relation between the control blood pressure of the rat and the incidence of pressor effects of heparinized human plasma. The clear rectangles represent positive or pressor effects, the inside figures give the percentage of the total. The shaded rectangles represent negative effects.

of the control blood pressure, the depth of anesthesia, the volume of fluid injected prior to the injection of the plasma under study, the order of injection of various hemodynamic (plasma and epinephrine) and indifferent solutions, the vasomotor reactivity of the rat and the unequal concentrations of pressor substances in human plasma at different times. In order to evaluate the rôle of some of these factors.

the experimental records have been analyzed carefully from several angles

The level of the rat's blood pressure prior to the initial injection of heparinized plasma seemed to have little effect on the response if it

TABLE 4—Results of Repeated Experiments with Plasmas from the Same Patients\*

Patient	Age	Diagnosis	Date	Rat	Plasma		Saline Solution		Anesthesia	Clinical Condition
					Control Blood Pressure, Mm Hg	Pressor Effect	Control Blood Pressure, Mm Hg	Pressor Effect		
J G	63	HH	3/22/33	20	137	0(1)			Deep	
			4/21/33	42	108	0(1)			Deep	Unchanged
			6/23/33	69	115	8(1)	111	11(1)	Light	Unchanged
			12/ 1/33	121	122	10(2,S)	132	0(2)	Light	Unchanged
C W	50	HH	4/ 3/33	29	110	0(2)			Deep	
			6/ 5/33	60	118	13(1)	128	5(2)	Light	Unchanged
R S	26	NH	5/ 3/33	50	136	4(1)			Deep	General edema
			6/13/33	65	126	12(1)	12c	7(1,S)	Light	No edema
E B	51	NH	5/18/33	53	126	9(1)			Deep	Acute colitis
			10/ 2/33	85	140	6(1,S)	14*	0(1)	Light	Acute heart failure
			10/ 3/33	86	142	8(1,S)	141	11(1,S)	Light	Unchanged
			1/11/34	135	146	10(2)	142	0(2)	Light	Chronic heart failure
C B	46	MH	5/25/33	57	114	9(1)	104	0(1)	Deep	
			5/31/33	58	84	12(1,S)			Light	Unchanged
K B	39	UH	6/28/33	72	126	10(1,S)	107	5(1)	Light	
			9/26/33	84	154	6(1,S)	156	7(1,S)	Light	Unchanged
E A	50	HH	9/15/33	78	114	10(1,S)			Light	
			10/12/33	92	122	20(2,S)	114	12(1,S)	Light	Unchanged
			2/16/34	150	134	0(2)			Light	Unchanged
			11/ 6/34	163	154	7(1)	148	0(1)	Light	Unchanged
E H	43	HH	11/ 7/33	107	136	7(2)	125	10(1,S)	Light	Early heart failure
			1/ 9/34	133	142	5(2)	136	14(2,S)	Light	Coronary occlusion
			1/31/34	143	128	6(2)	124	0(2)	Light	Severe heart failure
W M	25	HH	11/10/33	110	120	12(2,S)			Light	
			11/17/33	114	123	0(2)	125	11(1)	Light	Unchanged
H P	23	MH	11/24/33	117	104	15(2,S)	104	12(2)	Light	Uremia, acute neuroretinitis
			12/ 4/33	122	120	8(2,S)	116	7(2)	Light	Unchanged
			1/10/34	134	132	4(2)			Deep	Acute heart failure
A S	50	HC	1/30/34	142	131	15(2,S)	128	0(2)	Light	
			2/ 1/34	144	128	14(2)	135	8(2)	Light	Unchanged
J H	41	MD	10/29/34	159	131	0(1)	131	0(1)	Light	
			10/30/34	160	156	7(2)	156	0(1)	Light	Unchanged
I W	21	HC	10/30/34	160	156	8(2)	156	0(1)	Light	
			10/31/34	161	138	6(2)	120	0(1)	Deep	Unchanged

\* Explanation of the symbols is given in the footnotes to table 2

lay above 100 mm of mercury, which was the case in 89 per cent of the experiments. However, in rats with a blood pressure of 100 mm or less, there was a higher incidence of positive or pressor effects, as shown in figure 3. If the significance of this difference could be



doubted because of the small number of experiments, confirmatory evidence was found in the experiments in which, for one reason or another, the rat's blood pressure dropped from a normal level to a considerably lower one. In 17 rats which had given little or no response to plasma injected at the normal level of blood pressure, pressor effects were obtained with injections at the hypotensive level. Details are given in table 3. The fact that with either initial or late hypotension the pressor effect of injected plasma was likely to be sustained suggested a beneficial increase in the circulating blood volume as the direct cause of the positive result.

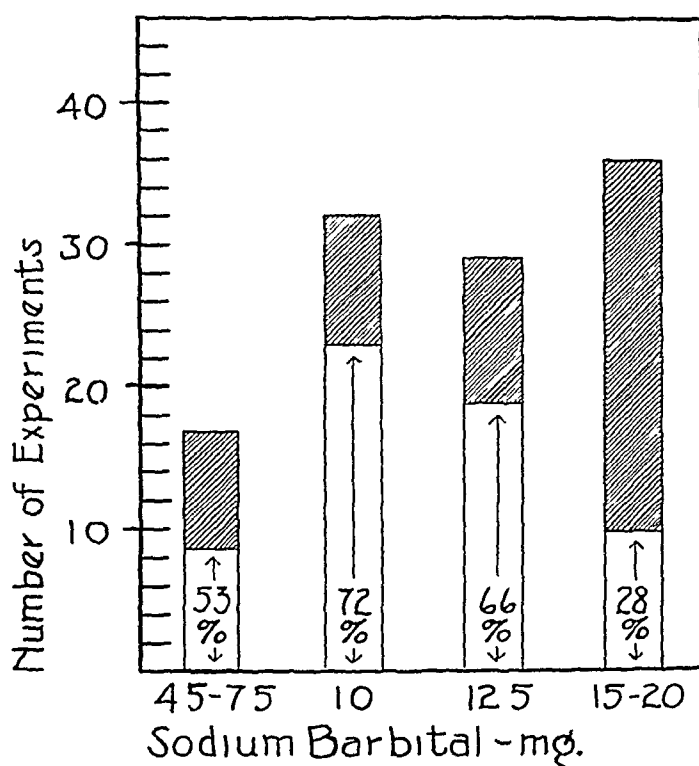


Fig 4—The relation between the amount of anesthetic (sodium barbital) and the pressor effect of heparinized plasma in the rat. The clear rectangles represent positive or pressor effects, the inside figures give the percentage of the total. The shaded rectangles represent negative plasmas.

The rôle of anesthesia is indicated in figure 4. When the amount of sodium barbital exceeded 15 mg., the number of experiments without pressor effects from plasma was about three times the number of experiments showing pressor responses. In contrast, the negative results were only half as numerous as the positive results when the dosage of sodium barbital was between 5 and 15 mg. Variation in the amount of anesthetic used may well have been a factor in the dissimilar response of different rats to samples of plasma from the same patient. This is illustrated in table 4.

The volume of fluid given intravenously prior to the first injection of heparinized plasma might be considered as a factor in the rat's response to plasma, because of the small blood volume of the animal and the possible change in the depth of anesthesia and vasomotor reactivity during a number of five to fifteen minute intervals between injections. Of 69 rats into which plasma was injected first, only 20 showed a pressor effect, while 22 of 35 rats given 2 cc of saline solution or solution of epinephrine prior to the first injection of plasma gave a pressor response to the latter. This would seem to indicate that a moderate increase in the rat's blood volume may be a helpful factor in the pressor response to plasma. That this is not entirely true is shown by the regular decrease in response to successive administrations of plasma after the first pressor effect and by the failure of the second or third injection of plasma to produce an elevation in blood pressure if the first dose had no effect. Furthermore, the 69 rats given plasma on the first injection happened to include 29 rats which had received more than 15 mg of sodium barbital, or 85 per cent of the rats with the deepest anesthesia. This circumstance, as discussed in the preceding paragraph, would of itself tend to reduce the number of positive, or pressor, results in this series.

The order of injection of hemodynamic solutions, such as plasma, epinephrine or plasma plus epinephrine, was varied in different experiments. Of 6 rats given epinephrine in saline solution prior to the first injection of plasma, 4 showed no response to plasma and 2 had a rise of only 5 mm. All of them had reacted well to epinephrine. In 15 other rats, epinephrine in saline solution or plasma plus epinephrine or both were injected after the first dose of plasma. After the usual interval, another injection of plasma was given. In none of these experiments was the reaction to the postepinephrine injection of plasma greater than the response to the first, or preepinephrine, injection of plasma. In other words, there was no evidence that the previous intravenous administration of epinephrine in an amount sufficient to produce a typical rise in blood pressure heightened the vasomotor reactivity of the rat to heparinized human plasma. Furthermore, in 24 rats the rise in blood pressure produced by a given dose of epinephrine, usually 0.0005 mg, in physiologic solution of sodium chloride, was compared with the pressor effect of the same amount of epinephrine in heparinized plasma. Other variables were carefully controlled. The average rises in blood pressure were 12.4 and 13.6 mm, respectively. Epinephrine in plasma tended to give slightly more prolonged pressor effects than epinephrine in physiologic solution of sodium chloride. Eleven of the 24 rats received injections of plasmas which caused pressor activity. Hence, the group was a fair sample of the entire series. From these results there was no evidence of a synergistic action

in the rat between the plasmas from hypertensive patients and the minimal effective doses of epinephrine

The vasomotor reactivity of the rat was tested in two ways, by means of epinephrine and by the injection of physiologic solution of sodium chloride. The injection of epinephrine was carried out in 98 of the 131 rats. The minimal effective dose corresponded to about 0.0008 mg per kilogram of body weight per minute, when injected at the rate of 1 cc per minute of a 1:4,000,000 solution in physiologic solution of sodium chloride, freshly prepared by diluting the commercial 1:1,000 solution. A definite depressor effect was never observed. Epinephrine, in contrast to saline solution or plasma, never caused a sustained rise in blood pressure at the ordinary levels.

The control injection of physiologic solution of sodium chloride, in amounts of 1 or 2 cc, was performed in 77 rats. The control levels of blood pressure after the injections lay at 101 mm of mercury or above in 91 per cent of the experiments, as was true following the injections of plasma. A rise in blood pressure occurred in 42 rats, but in only 9 of these was there no effect from heparinized plasma. The coincidence of such factors as jerking of the lightly anesthetized animals, failure of the blood pressure to return to the control level after the injection ("sustained" rise) and difficulty in the interpretation of the graphic record for 8 of the 9 rats should eliminate this group from serious consideration as an exception to the general result that rats responded with a pressor effect to plasma whenever they reacted positively to the more temporary increase in blood volume produced by saline solution. In 13 rats the blood pressure was unaffected by either plasma or saline solution. Of the 31 rats that gave pressor response to both plasma and saline solution, the records for 25 were satisfactory for further analysis. Here again, about 90 per cent of the control levels of blood pressure were above 100 mm of mercury, and 40 per cent lay between 121 and 140 mm. Simple averaging of the rises in blood pressure produced by the injection of 0.9 per cent saline solution or plasma resulted in an identical figure for both, 11 mm. However, careful study of the records of the individual experiments revealed that saline solution was injected first in 19 of the 25 rats, that the rise was "sustained" in 13 of the 19 animals but in only 1 of the remaining 6, that plasma produced a "sustained" rise in only 6 of the 13 experiments in which there was a "sustained" response as the initial effect of the saline solution, and that the pressor effect of saline solution exceeded the pressor effect of plasma in only 2 of the 25 animals if the two factors just mentioned were taken into account, while the pressor effect of plasma surpassed the pressor effect of saline solution in 11 experiments, including 8 in which saline solution was injected first. From these

results it was apparent that the "control" injection of saline solution was not a true control if given at the very beginning of the experiment because it tended to produce an exaggerated rise of blood pressure, which, since it was "sustained" in two thirds of the animals, strongly suggested an increase of a temporarily diminished circulating blood volume as the cause of the observed pressor effect. The conclusion was strengthened by the occurrence of pressor effects of plasma at low levels of blood pressure (below 100 mm of mercury) in all of 11 rats tested which had previously given no response to plasma at higher or normal levels of blood pressure (table 3). In 5 of these rats the pressor effect at the hypotensive level was "sustained." A characteristic feature of the "sustained" effect, whether produced by saline solution or by plasma, was the magnitude of the rise, usually from 10 to 20 mm.

The analysis of 17 experiments in which heparinized plasma gave a pressor effect while saline solution produced no change in the blood pressure revealed that in 4 rats the plasma was injected first, however, the rise was "sustained" in only 1 of these. Of the other 13 rats, 5 gave a "sustained" response to plasma injected in amounts of 2 cc. The clinical material represented in this series of 17 experiments included 8 cases of "benign" hypertension and its sequels, 2 cases each of "malignant" hypertension and glomerulonephritic hypertension, 1 case of arteriosclerotic hypertension and 4 of nonhypertensive conditions. In other words, there was nothing remarkable about the clinical sources of the samples of plasma.

Possible variations in the concentration of the pressor substances in the plasma of a given patient at different periods were investigated by means of repeated experiments with plasma from 22 patients (table 4). The interval between the taking of samples varied from twenty-four hours to one year. In 11 cases the results were constant, and in 6 of the remaining 11 there were sufficient differences in the depth of anesthesia or in the control levels of the blood pressure of the rat to account for observed inconsistencies. Marked changes in the patient's clinical condition seemed to have much less influence on the experimental result than the state of the various rats used. On the whole, plasma from a given patient tended to produce constant effects. However, a much larger series of multiple experiments would be necessary to allow a definite conclusion on this point.

#### COMMENT

The search for a chemical pressor substance in the blood of hypertensive patients is not new. Janeway in 1913<sup>2</sup> reviewed the earlier experiments critically and discarded the hypothesis that epinephrine was responsible for clinical hypertension. As to pressor effects in

general, the experiments of Stewart<sup>7</sup> gave negative results, but the amount of human serum injected into dogs was undoubtedly too low. Danzer, Brody and Miles<sup>8</sup> reported positive or pressor results with whole blood injected into cats. The somewhat similar experiments of Curtis, Moncrieff and Wright<sup>9</sup> led to the opposite conclusion. Høst<sup>10</sup> performed many transfusions of blood from hypertonic subjects to patients with normal blood pressure without observing any significant effects on the blood pressure of the latter.

It required the work of Bohn<sup>4a</sup> to give a new impetus to the search for pressor substances in the blood of hypertensive subjects. In 1931 he reported that alcoholic extracts of whole blood from 100 normal persons and 84 patients with "red" hypertension caused a 10 to 20 mm fall in the blood pressure of curarized cats which had received ethyl carbamate (urethane). On the other hand, similar extracts of blood from 19 patients with "pale" hypertension ("malignant" nephrosclerosis) produced a rise in blood pressure of from 10 to 20 mm when injected intravenously into cats. There were admittedly difficulties in these experiments, since depressor effects occurred in one test or another in half of the patients with "pale" hypertension. Pressor effects were also obtained with extracts of plasma from 10 patients with "transitional" (i. e., from "red" to "pale") hypertension, from 7 of 10 patients with acute diffuse glomerulonephritis and from a number of patients with chronic hypertensive glomerulonephritis and uremia. In general, therefore, these results corroborated Volhard's<sup>5</sup> theoretical speculations on the etiology of clinical hypertension.

Repetition of Bohn's work by other investigators has led to conflicting results. Marx and Hefke<sup>11</sup> reported prolonged rises in the blood pressure of from 15 to 45 mm of mercury in trained unanesthetized dogs into which were injected alcoholic extracts of from 80 to 100 cc of blood from patients with "malignant" hypertension. The maximum response occurred with extracts of blood from patients with acute nephritis or contracted kidneys. Unfortunately, similar results were also obtained with extracts of blood from epileptic patients.

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7 Stewart, G. N. So-Called Biological Tests for Adrenalin in the Blood, with Some Observations on Arterial Hypertonus, *J. Exper. Med.* **14** 377, 1911.

8 Danzer, C. S., Brody, J. G., and Miles, A. L. Existence of Pressor Substance in Blood of Clinical Case of Hypertension, *Proc. Soc. Exper. Biol. & Med.* **23** 454, 1926.

9 Curtis, F. R., Moncrieff, A. A., and Wright, S. Supposed Presence of Pressor Substance in Blood of Patients with High Blood Pressure, *J. Path. & Bact.* **30** 5, 1927.

10 Høst, H. F. Experimental Investigations of Hypertonia, *Acta med. Scandinav.* **77** 28, 1931.

11 Marx, H., and Hefke, K. Untersuchungen zur Pathogenese der Hypertonie, *Klin. Wchnschr.* **12** 1318, 1933.

There was no direct correlation between the height of the patient's blood pressure and the amount of pressor effect. A carefully conducted series of experiments by de Wesselow and Griffiths,<sup>12</sup> in which various methods of extraction were used, led the authors to conclude that the first effect of all extracts of whole blood was a rapid fall in the blood pressure of cats, that the pressor effects of extracts of whole blood were the same for normal persons and for donors with "malignant" hypertension and scarcely differed from the slight rise following the injection of 5 cc of Tyrode's solution, and that extracts of whole blood from patients with "benign" hypertension gave the most marked pressor results. However, extracts of the plasma had no effects in the last group and, in general, were physiologically identical in the normal persons and in those with a pathologic condition. Ultrafiltrates of human plasma never showed pressor effects. In short, Bohn's conclusions were entirely contradicted, both as to fact and as to theory.

In a more recent publication, however, Bohn and Schlapp<sup>4b</sup> described an improved method for extracting human plasma to get rid of depressor substances and laid down strict conditions for the rest of the experimental procedure in order to control the depth of anesthesia, the initial level of the cat's blood pressure, the number and nature of solutions injected and other variables. Strongly pressor effects were again reported from plasma of patients with "malignant" hypertension and chronic nephritis, but early depressor, with later pressor, effects were present in the plasma of patients with acute nephritis, before eclampsia and during eclampsia. Contrasting with these results are the thorough studies of Page<sup>13</sup> and of Capps, Ferris, Taylor and Weiss<sup>14</sup>. Page has detected a powerful pressor substance in extracts of the plasma and other body fluids of human subjects without observing an increased amount in the plasma of patients with various types of hypertension. Capps and his associates have worked with acetone and alcohol fractions of both the blood and the urine of normal and hypertensive persons. The extracts of blood produced no significant pressor effect, regardless of the clinical source. The urinary extracts usually contained pressor material, but there was no significant difference between the normal and the hypertensive subject in respect to the quantity of pressor substance excreted. Elliott and Nuzum,<sup>15</sup> who injected citrated human

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12 de Wesselow, O L V S, and Griffiths, W J. On the Question of Pressor Bodies in the Blood of Hypertensive Subjects, *Brit J Exper Path* **15** 45, 1934

13 Page, I H. The Nature and Action of a Pressor Substance Found in Body Fluids of Man, *J Clin Investigation* **13** 703, 1934

14 Capps, R B, Ferris, E B, Taylor, F H L, and Weiss, Soma. Rôle of Pressor Substances in Etiology of Arterial Hypertension, *Proc Soc Exper Biol & Med* **31** 1106, 1934

15 Elliott, A H, and Nuzum, F R. Possibility of Pressor Principle in Blood of Persons with Hypertension. Experimental Study, *J Lab & Clin Med* **18** 1255, 1933

blood into rabbits, also failed to observe striking differences in vaso-motor effects between blood from normal and that from hypertensive persons

The present study has been in progress since 1932. At first, 12 trained unanesthetized dogs were used. Their blood pressure was recorded directly from the transplanted common carotid or femoral artery, according to the method of Dragstedt<sup>16</sup>. Heparinized plasma of human blood was injected intravenously in amounts varying from 4 to 20 cc. The samples of blood came from 31 patients with various types of hypertension, including 7 in the "malignant" stage. Plasma from 16 nonhypertensive patients was also tested. The results were entirely negative in all but 4 instances and in only 1 of these was plasma used from a patient with "malignant" hypertension. Repeated experiments were carried out with the plasma of 3 patients with "malignant" hypertension. The factor of dilution of the patient's blood by the dog's blood volume was naturally considered as the most likely explanation for the absence of pressor effects. Hence, the rat was chosen as the experimental animal for the remainder of the work. Incidentally, it was possible to confirm Dragstedt's<sup>16</sup> observations in regard to the minimal effective dose of epinephrine and the absence of a depressor response in the unanesthetized dog.

The results of the injection of heparinized human plasma into rats have already been discussed in some detail. Critical consideration of the experimental procedure reveals serious drawbacks, e. g., the small blood volume of the rat and the danger of overloading the circulatory system by even a few injections, the possible delayed toxic effect of foreign protein, the difficulty of controlling the degree of anesthesia and respiratory ventilation and the absence in all but the last 12 experiments of comparative observations on injections of different plasmas in the same rat. However, in spite of these and other difficulties, there is no doubt that the pressor effect in the rat of plasma from a patient with "malignant" or "pale" hypertension is indistinguishable from the pressor effect of plasma from a patient with a nonhypertensive condition or "benign" hypertension. Furthermore, the percentage of positive results was about the same for all clinical groups (table 1). That the positive or pressor response must be interpreted in relation to the animal's circulating blood volume, level of blood pressure and depth of anesthesia has already been demonstrated. The previous injection of epinephrine seems to have little bearing on the later response of the rat to human plasma. It is important, however, to rule out volume effects on the blood pressure by preliminary injections of saline or other solutions until the

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16 Dragstedt, C. A. Observations on Hemodynamic Action of Epinephrine  
J. A. M. A. 91:1033 (Oct. 6) 1928

blood pressure is stabilized. This undoubtedly applies to other animals as well as to the rat, especially when a general anesthetic is employed and the experiment is prolonged.

The pressor effect in the rat of heparinized human plasma is not dramatic. In terms of epinephrine it would correspond usually to a minimal effective dose. Of course, the material injected has been diluted from ten to thirty times by the rat's own blood. Judging from the extreme rarity of immediate depressor effects, human plasma is not toxic to the rat. In fact, in a number of animals in which the blood pressure had dropped to low levels during the course of an experiment, the repeated injection of plasma or packed red corpuscles from human blood or mixtures of the two has resulted in a return of the blood pressure to a normal level and marked improvement in the general condition of the rat.

The nature of the pressor substance apparently present in many human plasmas has not been investigated in this study. Chemical treatment of the plasma was purposely avoided. Ultrafiltration was not attempted because of the uniformly negative results reported by other investigators. The difference between temporary and "sustained" pressor responses could not be traced to any known difference in the clinical source of the material. Plasma mixed with epinephrine usually produced no greater or less rise in the blood pressure than the control reaction to epinephrine in saline solution. Therefore, the pressor material in human plasma is not a sensitizer to epinephrine in the rat.

Whether the pressor activity is a constant or variable feature of the plasma of certain persons with or without hypertension has not been definitely established in this work. It is possible that repeated testing with plasma which originally caused a negative effect might yield positive results in some experiments. The interpretation of such variations is rather subjective, because of the difficulty in controlling conditions in the experimental animal. The old advice of Stewart<sup>7</sup> to "fractionate" the test object or the material tested is very timely.

One may conclude from the experiments reported here that no evidence has been obtained to support the views of the Volhard group that the etiology of "pale" hypertension is intimately related to a pressor substance in the circulating blood of the diseased person. On the contrary, an apparently identical pressor effect is produced by plasma from patients with "benign" hypertension or with normal blood pressure. Whether the pressor action of heparinized plasma in the rat is caused by the same material which other investigators have studied in various extracts of whole blood, plasma, urine or other body fluids has not been determined, but it is reasonable to assume that a common agent is involved in all these experiments. The more important question of the



rôle of such pressor substances in human cardiovascular physiology cannot be answered at present without unjustifiable speculation

#### SUMMARY

In preliminary experiments the intravenous injection of heparinized plasma of human blood into unanesthetized dogs produced no significant changes in the mean blood pressure, directly recorded. No difference was observed between the effects of plasma from nonhypertensive persons and the effects of plasma from "malignant" hypertensive patients.

The use of the rat as the test animal, to diminish the dilution of the injected plasma by the animal's blood volume, made possible the demonstration of pressor effects from 51, or 44 per cent, of 117 heparinized plasmas.

The distribution of pressor effects of the plasmas among the different clinical groups was independent of the type of hypertension or of the presence of hypertension.

Plasmas from 17 patients with "malignant" hypertension gave no higher incidence of pressor effects or greater rises in blood pressure than plasmas from 100 other subjects, of whom 83 had various types of hypertension and 17 had miscellaneous nonhypertensive conditions.

Plasmas from hypertensive patients did not increase the response of the blood pressure of the rat to minimal effective doses of epinephrine.

As a result of this study and the related work of other investigators, it must be concluded that there is no satisfactory evidence for the theory that "malignant" or "pale" hypertension (or, for that matter, any common form of clinical hypertension) is caused by the presence of pressor substances in the patient's blood.

# RELATIVE VALUES OF CAFFEINE AND HYPERTONIC DEXTROSE AND SALINE SOLUTIONS IN REDUCING CEREBROSPINAL FLUID PRESSURE

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The intravenous injection of a hypertonic solution of dextrose for the purpose of reducing the cerebrospinal fluid pressure is a common procedure in the treatment of neurologic disturbances, although few direct observations of its effects have been reported in the literature. The procedure is based mainly on a number of experimental studies on animals<sup>1</sup>

During exploratory craniotomy, Fay<sup>2</sup> observed a decrease in the dural tension following the intravenous administration of a 15 per cent saline solution. A number of observers have measured the effect of these solutions by the application of a tambour next to postoperative cranial defects or herniations, but their results are contradictory. Ebaugh and Stevenson<sup>3</sup> noted a prolonged fall in pressure after the

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From the Neurological Service of Dr Israel Strauss at the Mount Sinai Hospital

1 (a) Weed, L H, and McKibben, P S Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injection of Solutions of Various Concentrations, *Am J Physiol* **48** 512 (May) 1919, (b) Experimental Alterations in Brain Bulk, *ibid* **48** 531 (May) 1919 (c) Weed, L H, and Hughson, W Systemic Effects of the Intravenous Injection of Solutions of Various Concentrations, with Especial Reference to the Cerebrospinal Fluid Pressure, *ibid* **58** 53 (Nov) 1921, Spinal Fluid Pressure in Relation to the Bony Encasement of the Central Nervous System as a Rigid Container, *ibid* **58** 85 (Nov) 1921, Intracranial Venous Pressure and Spinal Fluid Pressure as Affected by Intravenous Injection of Solutions of Various Concentrations, *ibid* **58** 101 (Nov) 1921 (d) Sachs, E, and Malone, J Y The Use of Hypertonic Salt in Experimentally Increased Intracranial Pressure, *ibid* **55** 277, 1921 (e) Howe, H S Experimental Studies in the Reduction of the Normal Cerebrospinal Fluid Pressure in Cats, *A Research Nerv & Ment Dis, Proc* **4** 220, 1926 (f) Milles, G, and Hurwitz, P Effect of Hypertonic Solutions in Cerebrospinal Fluid Pressure with Special Reference to Secondary Rise and Toxicity, *Arch Surg* **24**.591 (April) 1932 (g) Ernst, Max Untersuchungen über die Wirkung anisotonischer Lösungen auf Gehirn und Liquor, *Deutsche Ztschr f Chr* **226** 222, 1930

2 Fay, T The Administration of Hypertonic Salt Solutions for the Relief of Intracranial Pressure, *J A M A* **80** 1445 (May 19) 1923

3 Ebaugh, F G, and Stevenson, G S Measurements of Intracranial Pressure Changes in an Epileptic and Its Experimental Variations, *Bull Johns Hopkins Hosp* **31**.440 (Dec) 1920

intravenous administration of 200 cc of a 30 per cent dextrose solution, while Stevenson and his associates<sup>4</sup> noted only a slight effect. Foley<sup>5</sup> used a 15 per cent saline solution and observed a definite decrease of the herniation. The more direct method of continuously measuring the spinal fluid pressure by means of lumbar puncture and a manometer has been applied more recently. With this technic, Foley<sup>5</sup> noted a marked fall with the administration of 190 cc of a 15 per cent saline solution, Browder<sup>6</sup> noted both a moderate fall and a distinct rise with 100 cc of a 50 per cent dextrose solution, and Haug<sup>7</sup> reported only a slight indefinite change caused by either solution. Milles and Hurwitz,<sup>1f</sup> Jackson and his co-workers<sup>8</sup> and Masserman<sup>9</sup> observed a primary transient rise, a secondary reduction and, finally, a tertiary rise above the normal a short time (from one-half to three hours) after the intravenous injection of up to 200 cc of dextrose solution. By a similar technic Denker<sup>10</sup> and Haug<sup>7</sup> demonstrated a constant decrease of the cerebrospinal fluid pressure for about one half hour following the intravenous injection of caffeine.

Since the common procedure in the clinical use of dextrose is to inject about 50 cc of a 50 per cent solution, more or less rapidly, intravenously with a syringe, and since saline solutions have not been sufficiently employed, the problem appeared to require further investigation. Furthermore, no observations have been reported in patients with increased intracranial pressure. The purpose of this report is to record the results of a study of the effect on a number of persons with normal and abnormal cerebrospinal fluid pressure when hypertonic solutions of dextrose and sodium chloride and of caffeine were administered intravenously in a short period of time.

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4 Stevenson, L., Christensen, B., and Wortis, S. B. Some Experiments in Intracranial Pressure in Man During Sleep, *Am J M Sc* **178** 663 (Nov) 1929

5 Foley, F. D. B. Clinical Uses of Salt Solutions in Conditions with Increased Intracranial Tension, *Surg, Gynec & Obst* **33** 126 (Aug) 1921

6 Browder, J. Dangers in the Use of Hypertonic Solutions in the Treatment of Brain Injuries, *Am J Surg* **8** 1213 (June) 1930

7 Haug, K. Klinische und pharmakodynamische Untersuchungen des Liquordrucks vermittelt Dauerdruckmessungen bei Geisteskranken, *Arch f Psychiat* **97** 189, 1932

8 Jackson, H., Kutsunai, T., Leader, L. O., and Joseph, L. D. Effects of Hypertonic Dextrose Solutions in Intracranial Pressure, *J A M A* **100** 731 (March 11) 1933

9 Masserman, J. H. Effects of Intravenous Administration of Hypertonic Solutions of Dextrose, *J A M A* **102** 2084 (June 23) 1934

10 Denker, P. G. The Effect of Caffeine on the Cerebrospinal Fluid Pressure, *Am J M Sc* **181** 675 (May) 1931

## METHOD

The study was carried out during routine tests by lumbar puncture on patients from the neurologic service of Dr Israel Strauss. The patients were chosen according to their ability to remain in the lateral position on the right side for the period required. The ages of the patients studied varied from 9 to 68 years. No sedative was administered, but as a reassuring preliminary measure the procedure was explained to the patient as much as possible. With local anesthesia, a lumbar puncture was made in the third lumbar space, and a glass manometer was attached with the loss of only 2 or 3 drops of fluid. A Queckenstedt test was performed to insure the patency of the system. Readings were then made until the basic normal variations were established, usually for from fifteen to thirty minutes. After this, the solution was injected into the median basilic vein with a large syringe, and the readings were continued at one minute (or more frequent) intervals for a varying period, as conditioned by the patient's cooperation. Before the termination of the examination the Queckenstedt test was repeated. The observation was discarded if the patient proved uncooperative, if the needle did not enter the subarachnoid space without mishap, if more than 2 or 3 drops of fluid was lost or if the cerebrospinal fluid system did not remain freely patent, as shown by the cardiac and respiratory oscillations and the Queckenstedt test. A total of fifty-one observations are reported (in some instances the same patient was used for more than one): fifteen with 50 cc of a 50 per cent dextrose solution, thirteen with 100 cc of a 50 per cent dextrose solution, seven with 50 cc of a 15 per cent saline solution, eight with 100 cc of a 15 per cent saline solution and eight with 5 grains (0.3 Gm) of caffeine sodium benzoate. The last group confirmed the findings of other workers and served as a control.

## OBSERVATIONS AND COMMENT

These observations are completely presented in charts 1 to 5. The ordinate unit represents 20 mm of cerebrospinal fluid pressure, and the abscissal unit, two minutes of time each. The perpendicular line preceding each reading denotes the preliminary variation of pressure taken as the basic standard. It is interesting that the extent of normal variations in the individual cases varied somewhat directly with the height of the pressure and was most marked in the cases of tumor of the brain. A significant fact is that in the cases of tumor of the brain there were wide rapid oscillations, even more striking than can be shown in a graph on such a small scale, this was most marked in the cases of the neoplasm of the posterior fossa (cases 25 and 50).

In most cases there was a rise in pressure preceding the injection, this was due to the application of the tourniquet. A primary rise in pressure following the injection was not a constant observation as reported by others<sup>11</sup>.

Chart 1 demonstrates the result of the administration of 50 cc of a 50 per cent solution of dextrose. The average duration of the injection

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11 Milles and Hurwitz<sup>12</sup> Jackson, Kutsunai, Leader and Joseph<sup>8</sup> Masserman<sup>9</sup>

tion was one minute and thirty-eight seconds. In only two cases (1 and 9) was there a slight lowering of the pressure, in ten cases, including one of tumor of the brain (2, 3, 4, 5, 10, 11, 12, 13, 14 and 15),

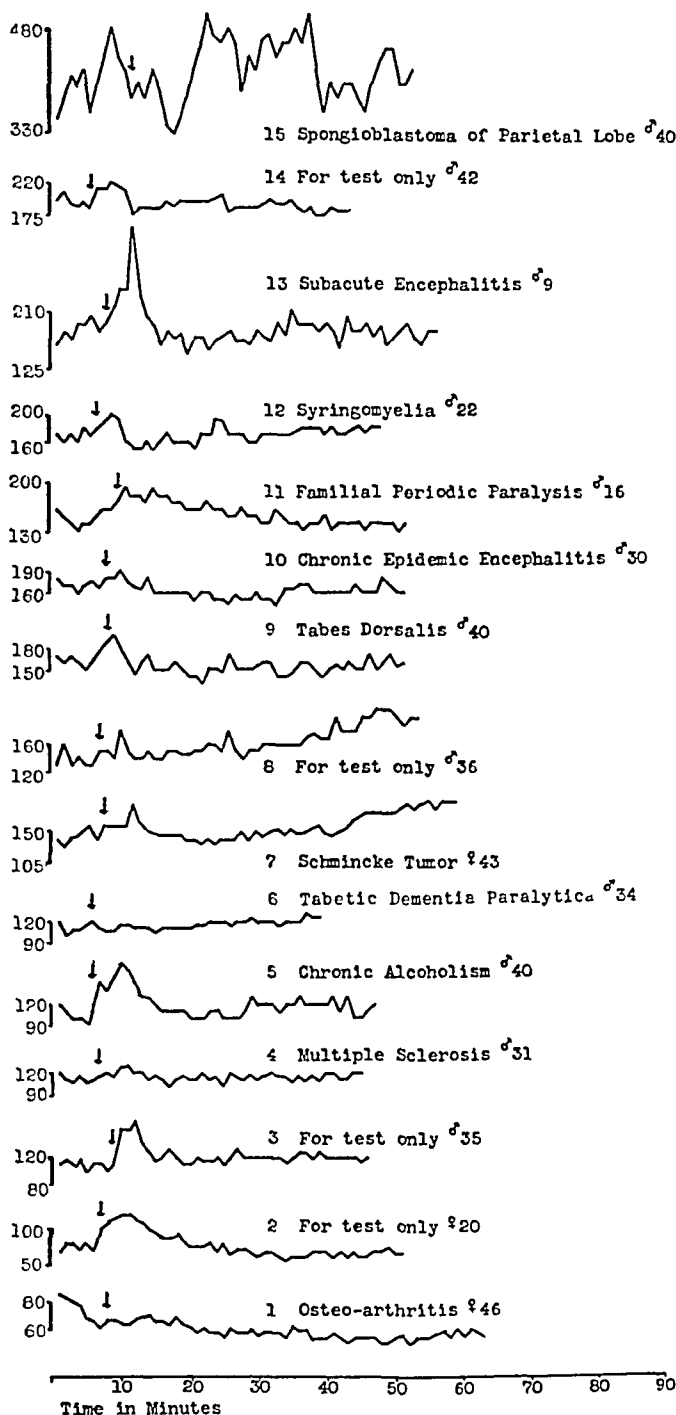


Fig 1 (cases 1 to 15) —The vertical lines indicate the extent of the preliminary variations in the cerebrospinal fluid pressure taken as the normal basic standard. The arrow marks the point of the intravenous injection of 50 cc of a 50 per cent solution of dextrose.

there was no significant change, while in three cases (6, 7 and 8) there was a definite rise. The injections of 100 cc of hypertonic solution of dextrose averaged two minutes and ten seconds each, and the obser-

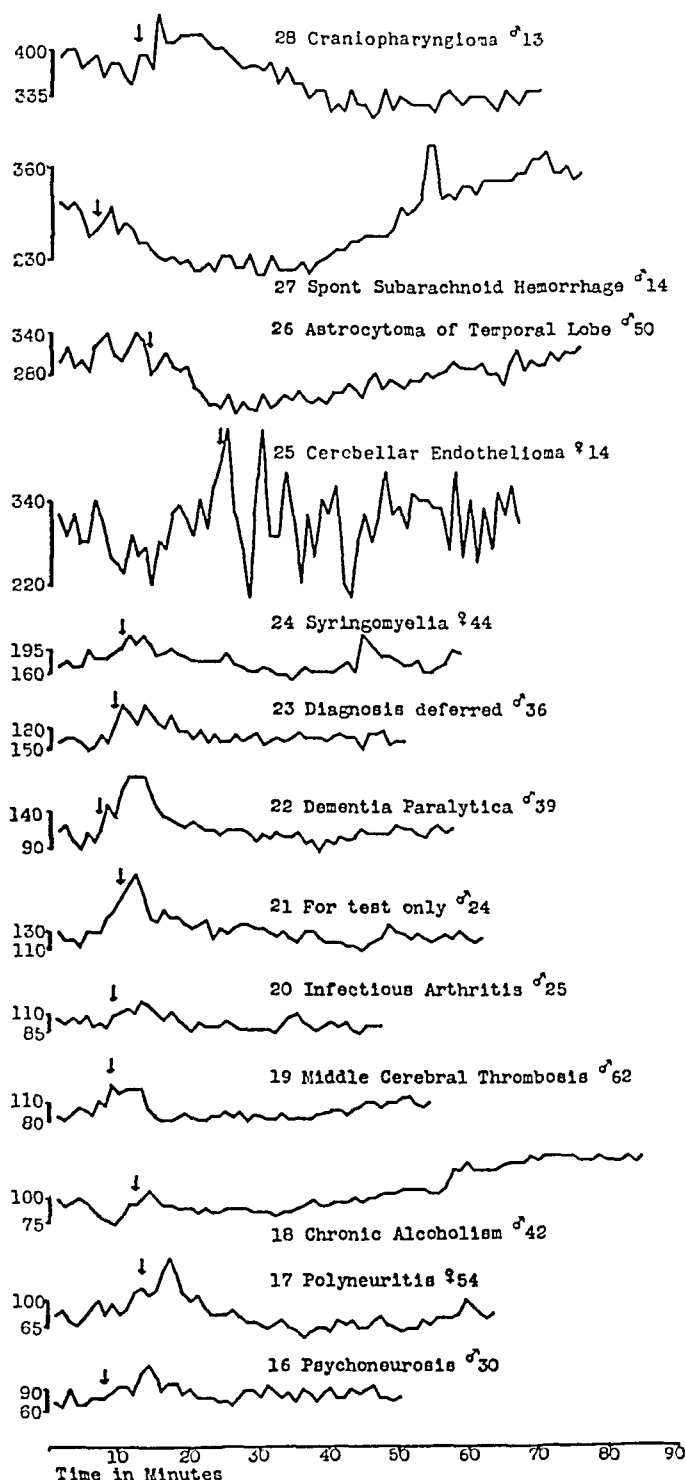


Fig 2 (cases 16 to 28) —The vertical lines indicate the extent of the preliminary variations in the cerebrospinal fluid pressure taken as the normal basic standard. The arrow marks the point of the intravenous injection of 100 cc of a 50 per cent solution of dextrose.

vations are shown in chart 2. A temporary fall occurred in only five cases (17, 24, 26, 27 and 28), three being cases of increased intracranial pressure. In seven cases, including one of tumor of the brain (16, 19, 20, 21, 22, 23 and 25), there was no appreciable effect, while in one case (18) there was a definite marked rise above the normal pressure.

The injection of hypertonic saline solution caused a definite decrease in the cerebrospinal fluid pressure in all the cases (charts 3 and 4).

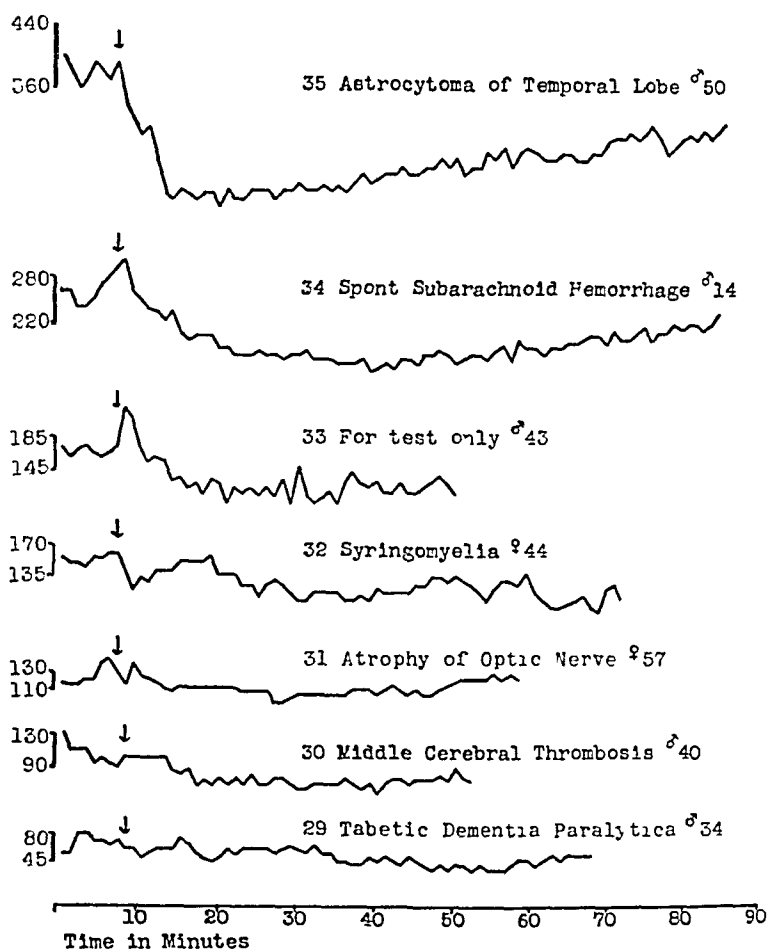


Fig 3 (cases 29 to 35) —The vertical lines indicate the extent of the preliminary variations in the cerebrospinal fluid pressure taken as the normal basic standard. The arrow marks the point of the intravenous injection of 50 cc of a 15 per cent solution of sodium chloride.

The average duration of the two doses was, respectively, two minutes, forty seconds and six minutes, forty seconds. With the doses of 50 cc the effect was temporary and was comparable to that noted in five cases in which 100 cc of hypertonic dextrose solution was injected, but a fall in pressure was constant. The reduction was also most marked in the cases of higher intracranial pressure. With 100 cc of a 15 per

cent saline solution a decrease of the cerebrospinal fluid pressure was observed in all cases, was the most marked in the series and persisted for the full length of the experiment

The depressant effect of caffeine on the cerebrospinal fluid pressure was confirmed (chart 5), but its duration was transient

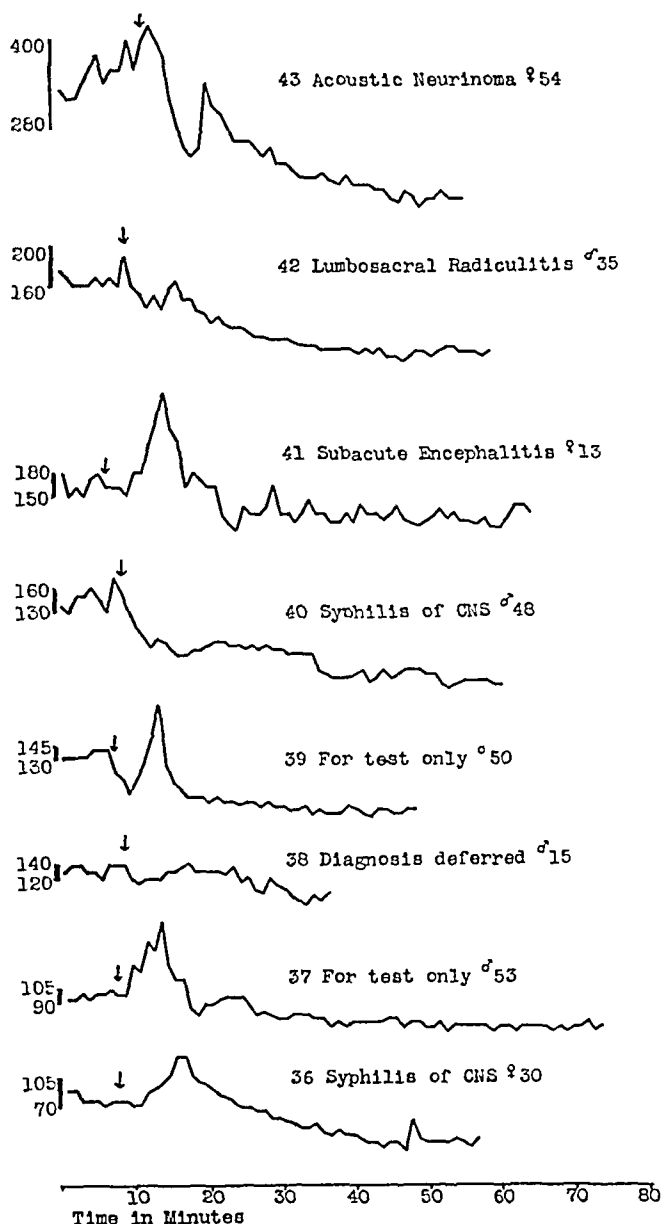


Fig 4 (cases 36 to 43) —The vertical lines indicate the extent of the preliminary variations in the cerebrospinal fluid pressure taken as the normal basic standard. The arrow marks the point of the intravenous injection of 100 cc of a 15 per cent solution of sodium chloride

An incidental observation was that when the pressure is decreased by any of the solutions the extent of the fluctuating variations is diminished and the pressure becomes more stable, when there is a return to the original pressure the full extent of the fluctuations recur



The most important fact in this study is that it demonstrates the superiority of a hypertonic solution of sodium chloride over that of a hypertonic solution of dextrose or caffeine as a depressant of the cerebrospinal fluid pressure. This is in agreement with the original observations of Weed and McKibben<sup>1a</sup> in animals, the solutions of

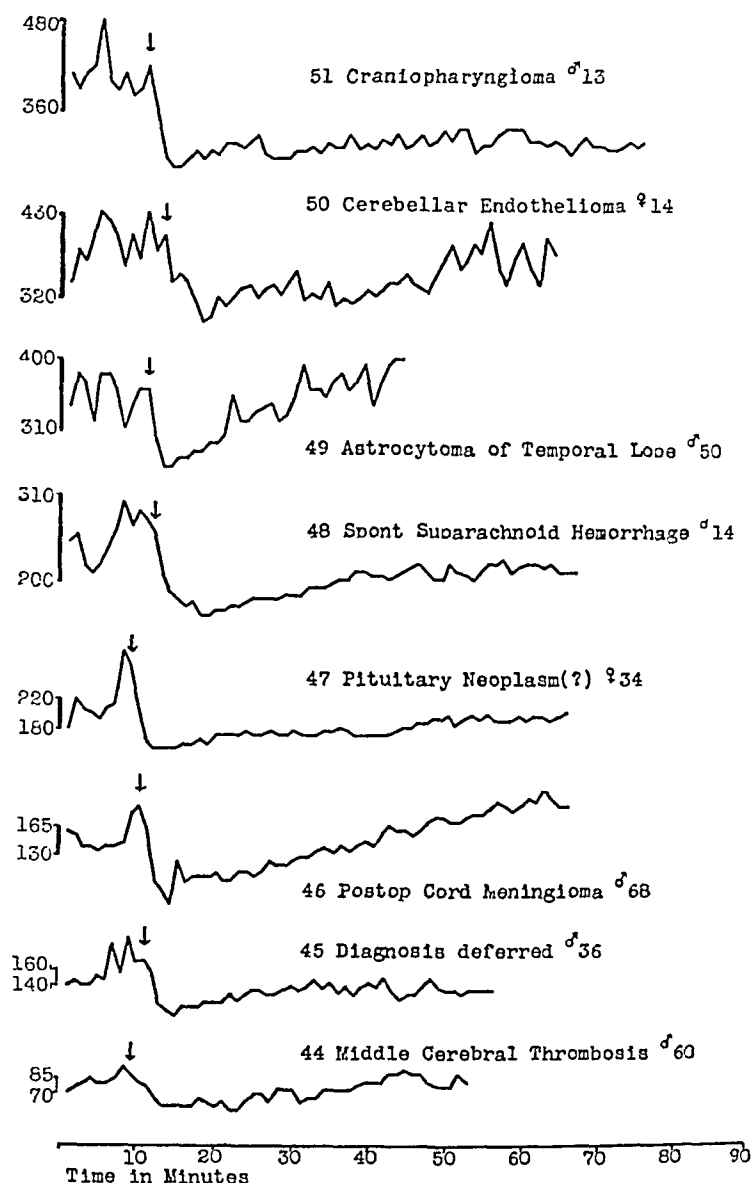


Fig 5 (cases 44 to 51) —The vertical lines indicate the extent of the preliminary variations in the cerebrospinal fluid pressure taken as the normal basic standard. The arrow marks the point of the intravenous injection of 5 grains of caffeine sodium benzoate.

dextrose caused a much smaller effect than did those of the electrolytes. This can be readily accounted for by the fact that the diffusion time of dextrose is three times that of sodium chloride and therefore its osmotic pressure is proportionately less.

It would seem that the saline solutions should displace the dextrose solutions in the clinical application of hypertonic solutions intravenously for the reduction of intracranial pressure. The dextrose solutions offer only slight beneficial effects and may be followed by an aggravation of the condition owing to the subsequent rise in pressure<sup>11</sup>. The toxic effect of hypertonic saline solution is doubtful. In none of the cases was a deleterious effect shown clinically, except for a transient flushing and a complaint of thirst. In two cases the injection was followed by a slight chill, but this was probably due to some pyrogenic impurity in the water<sup>12</sup>. In the treatment of thrombo-angitis obliterans with repeated injections of hypertonic (5 per cent) saline solution, Silbert<sup>13</sup> has not observed a fatality or a serious reaction in about twenty thousand such injections. The occasional report of adverse results must be attributed to the secondary rise in the cerebrospinal fluid pressure and should be applicable to any of the hypertonic solutions.

#### SUMMARY

The effects on the cerebrospinal fluid pressure of the intravenous administration of hypertonic dextrose (50 per cent) and saline (15 per cent) solution and a solution of caffeine sodium benzoate (5 grams) were compared in fifty-one observations on normal persons and on patients with increased intracranial pressure. The injection of dextrose solutions was effective in reducing the cerebrospinal fluid pressure in only relatively few cases. In a few cases the injection of a dextrose solution caused an immediate prolonged rise in the pressure. The effect of caffeine was greater and was consistent, but with both the latter and the dextrose the results were transient. The injection of hypertonic saline solution, however, resulted uniformly in a definite and more persistent reduction in the cerebrospinal fluid pressure. It is therefore suggested that hypertonic solutions of sodium chloride should replace the solutions of dextrose in clinical administration for the reduction of intracranial pressure.

12 Seibert, F. B. Fever-Producing Substances Found in Some Distilled Waters, *Am J Physiol* **67** 90 (Dec.) 1923.

13 Silbert, S. Thrombo-Angitis Obliterans (Buerger) V. Results of Treatment with Repeated Injections of Hypertonic Salt Solution, *J A M A* **94** 1730 (May 31) 1930.

# LYMPHOBLASTOMA CUTIS

## REPORT OF A CASE WITH AUTOPSY

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The generic name lymphoblastoma cutis, suggested first by Mallory, in 1914, and later by Keim,<sup>1</sup> in 1924, covers a group of dyscrasias of the skin, glands and blood which blend one into the other and are of such rarity and interest as to warrant reporting them. In this group are included Hodgkin's disease, lymphosarcoma, leukemia and mycosis fungoides. Goeckerman stated that there is a growing tendency in this country to regard them as varying clinical manifestations of the same disease. At least, his experience at the Mayo Clinic supported the conception that the diseases are genetically closely related. In some cases a condition with characteristics of one disease has later changed and developed characteristics of another or possibly of several others of the group. Occasional mention of such metamorphoses has been made in the literature. According to Arndt,<sup>2</sup> Eihlich and his pupil Pinkus were the first to show that lymphatic leukemia and pseudoleukemic processes were the same. Elsner<sup>3</sup> and Sternberg both stated that the transition of primary pseudoleukemia to leukemia is possible and occasionally occurs. Goeckerman and Montgomery<sup>4</sup> cited cases in which mycosis fungoides has changed to lymphosarcoma. They reported a case suggestive of this change. Bunting and Yates expressed the belief that lymphogranuloma can become transformed into sarcoma, and Warthin<sup>5</sup> maintained that it

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Read before the North Pacific Society of Internal Medicine, Seattle, March 17, 1934

1 Keim, H L. Universal Leukemia Cutis, Arch Dermat & Syph **10** 579 (Nov) 1924

2 Arndt, G. Diseases and New Growths of Lymphatic Origin, J A M A **63** 1268 (Oct 10) 1914

3 Elsner, H L. Prognosis of Internal Diseases, in Monographic-Medicine, New York, D Appleton & Company, 1916, vol 6, p 536

4 Goeckerman, W H, and Montgomery, H. Cutaneous Lymphoblastoma Report of Two Unusual Cases, Arch Dermat & Syph **24** 383 (Sept) 1931

5 Warthin, A S, in Osler, W, and McCrae, T. Modern Medicine, Its Theory and Practice, ed 3, Philadelphia, Lea & Febiger, 1925-1927, vol 1, pt 2, chap 6, p 199

can change into leukemia. Cases have been reported in which the condition could not be classified even after complete autopsy and on which different pathologists have expressed widely divergent opinions. Our case is interesting from the standpoint of the protean clinical manifestations and instructive from the standpoint of the pathologic changes.

#### REPORT OF CASE

*History*—The patient was first seen in August 1928, in consultation with Dr J E Ettelson, who made the diagnosis of lymphoblastoma cutis. She was a widow, 60 years of age. Her chief complaint was an itching eruption of the skin of two years' duration. It began in 1926 with two red, scaly patches on the inner side of the thighs and gradually spread to involve the entire skin. She felt well in every other way and complained of no symptoms referable to the gastrointestinal, genito-urinary, cardiorespiratory or nervous systems. Her entire skin was peeling and gave her almost intolerable discomfort from the intense itching. Her family and her personal history were entirely negative.

*Examination*—Physical examination revealed a well nourished and well preserved woman. There was a generalized, scaly, erythematous dermatitis. The color was dull red to reddish brown. The exfoliation was of a mild type with slightly adherent scales. The skin was thickened and firm to the touch. It had a pliable, leathery feel. The gluteal and other skin folds were greatly exaggerated. The results of examination of the heart and lungs and those of other physical examinations were entirely negative with the exception of the discovery of a moderate enlargement of the cervical and left axillary lymph glands, which were the size of small walnuts, firm, discrete and not tender. The liver and the spleen showed no perceptible enlargement. The roentgenogram of the chest showed no mediastinal enlargement or other pathologic changes. A complete gastro-intestinal roentgen examination, including a Cole-Graham study of the gallbladder, gave negative results. The basal metabolic rate was  $-3$ . The urine was entirely normal on several examinations. The acids of the stomach showed a free hydrochloric acid value of 39 and a total acidity of 66. The amount of bilirubin in the serum was normal. The Wassermann reaction was negative. The urea nitrogen content of the blood was 15.5 mg per hundred cubic centimeters, and the sugar content was 100 mg. The eyegrounds showed no changes.

The chief scientific interest in the patient at that time lay in the blood counts and the adenopathy. There was a persistently high lymphocyte count, ranging up to 79 per cent, with a highest total count of 26,000. A few lymphoblasts were consistently present. Table 1 is a record of the different blood counts made during the patient's stay in the hospital as well as of subsequent counts made frequently during the course of the disease.

*Pathologic Report*—Owing to the atypical blood count when the patient was first seen in 1928, it was deemed advisable to remove a gland for microscopic examination. This was done on Sept 8, 1928. The following is the pathologic report by Dr H H Fosskett:

"The specimen consisted of fragments of a lymph node measuring 2 by 4 cm with an overlying area of skin. It was of a soft, homogeneous consistency. Surfaces made by sectioning revealed a homogeneous, grayish, cellular tissue. The gland was smoothly encapsulated.

"Microscopic sections of the gland revealed hyperplasia of lymphoid cells somewhat larger than normal lymphocytes. This hyperplasia was of sufficient extent to obliterate all the normal markings of the lymph node. There was a peculiar proliferation of endothelial cells of the capillary walls. There were no mitotic figures. There was no evidence of fibrosis or hemorrhage. The skin showed an accumulation of lymphocytes in the subcutaneous tissues with a marked hyperplasia of the lymphoid tissue of the papillary layer of the skin. The hyperplasia consisted of an accumulation of lymphocytes, lymphoblasts and occasional plasma cells. There was no apparent thickening of the stratum corneum of the skin.

TABLE 1—*Record of Blood Counts Made During a Five Year Period*

Date	Red Blood Cells, Thousands	White Blood Cells	Hemo- globin, Per centage	Poly- morpho- nuclear neutro- phils, Per centage	Poly- morpho- nuclear eosino- phils, Per centage	Poly- morpho- nuclear Baso- phils, Per centage	Lym- pho- cytes, Per centage	Cells Not Classi- fied, Per centage	Lympho- blasts or Mono- nuclears, Per centage	Rieder- Cells, Per centage
8/31/28	4,700	18,700	93	25	1	1	68	5		
9/ 1/28		20,600		14	1		70	18		
9/ 2/28		18,200		18	2		79	1		
9/ 3/28		12,000		20			70	10		
9/ 4/28		16,400		17			74	8		1
9/ 9/28	5,200	26,000	100	24			70	6		
10/ 1/28	4,500	10,000	89	20	5		75			
11/12/28	4,600	13,000	90	26	3		70	1		
12/13/28	4,800	23,000	87	33	4		63			
3/11/29	4,900	14,000	100	38	2	1	59			
6/15/29	4,300	9,400		72			26		2	
7/ 8/29	4,700	6,600	95	64			34		2	
9/ 5/29	4,800	7,000	95	68	2		29	1		
11/12/29	4,900	7,000	90	64	1		28	2	5	
12/24/30	4,800	8,800	92	60	2		34		4	
3/21/31	5,200	6,700	100	58	1		38	3		
8/15/31	5,500	6,600	90	55	3		37	2	1	
1/ 8/32	3,900	4,800	88							
1/11/32		5,700		57	1		42			
9/19/32		7,250	91	64	1		35			
5/25/33	3,900	7,600	65	30	4		66			
5/26/33		8,500								
9/18/33		13,500		42	1		50		2	5

"The diagnosis is chronic lymphatic leukemia with hyperplasia of lymphoid cells involving both the lymph nodes and the cutaneous lymphoid tissue."

*Course*—The patient left the hospital in 1928 and was given no treatment other than local applications for the dermatitis and intramuscular injections of sodium cacodylate. During 1929, 1930 and part of 1931 she enjoyed good health and took several long motor trips. The exfoliative dermatitis disappeared, and the swelling of the glands subsided, but there was a red, glazed appearance of the skin of the face. Erythematous rashes appeared from time to time on the neck and chest. There was also mild pruritus. The spleen was never palpable. In the winter of 1931 the exfoliative dermatitis reappeared and continued throughout 1932 and 1933. Enlargement of the glands again appeared in the neck, axillae and groins. The exfoliation was so intense that each morning a cupful of scales was taken from the bed clothing. Neither injections of sodium cacodylate nor roentgen therapy affected the cutaneous lesions. In the spring of 1933 flat purplish-red tumor-like masses began to appear in the skin, first in the groins and then

under the breasts, in the popliteal space, about the umbilicus and in the gluteal folds (figs 1, 2 and 3) They varied from the size of a nickel up to the size of a quarter and were firm and not tender The erythema faded on pressure The epidermis over the growths was intact, although it was thin and glazed-looking The nodules increased in size and number up to the time of death but did not ulcerate

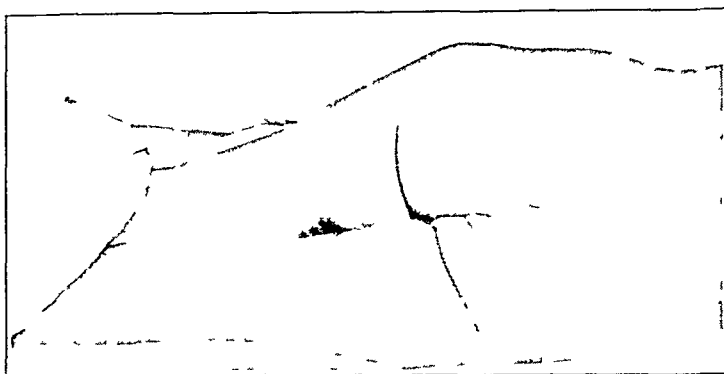


Fig 1—Tumor masses on posterior surface of both thighs Note the leathery texture of the skin and the deepened gluteal folds

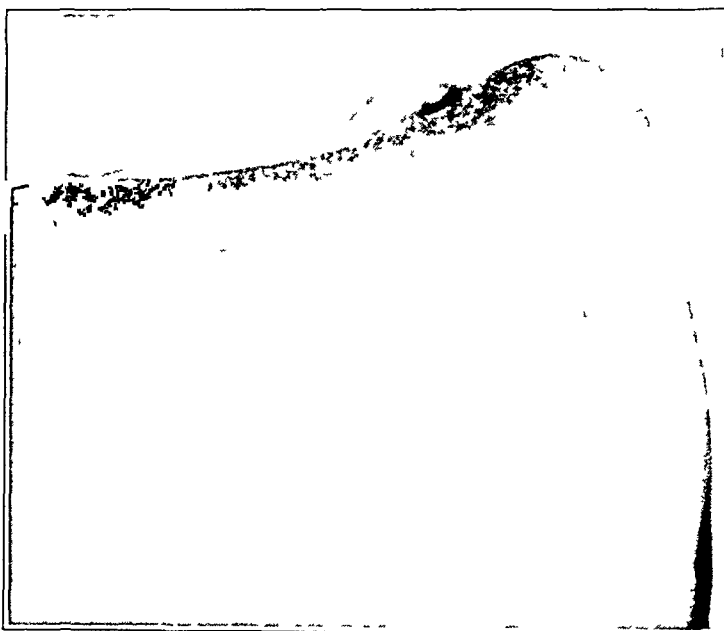


Fig 2—Photograph showing typical exfoliation and a cutaneous tumor in the left interscapular region

Coincident with the appearance of the tumors in the skin, the patient had a bout of high temperature resembling the Pel-Ebstein type of fever (fig 4) Her temperature rose as high as 106.4 F, with prostrating chills and drenching sweats, and would drop to subnormal within a few hours The fever lasted ten days It was accompanied by bloating and severe constipation The white blood cell count remained low, and all laboratory findings during the bout of fever were

negative, including those from blood cultures. Three months later she again showed fever, of a milder degree, which lasted until the time of her death, but this time there was an intractable diarrhea. Three weeks before her death the white blood cell count was 13,500, with 42 per cent polymorphonuclears, 50 per cent lymphocytes, 1 per cent eosinophils and 7 per cent lymphoblastic cells. In contrast to what was observed during the remission of the disease, the lymphocytic element had again become predominant. There were many immature cells with large nuclei containing several nucleoli and a thin ring of heavily staining protoplasm. These cells gave a negative reaction to peroxidase and were considered to be lymphoblasts.

Three weeks before death the patient began to fail rapidly. She lost weight and strength and showed an icteric pallor. She became bedridden. The cutaneous tumors became especially prominent about the umbilicus. The spleen showed a tremendous enlargement. It was hard, fairly smooth and very tender. It extended almost down to the umbilicus. The liver was barely palpable. On October 4 the patient complained of pain in the left hypochondrium on deep inspiration.

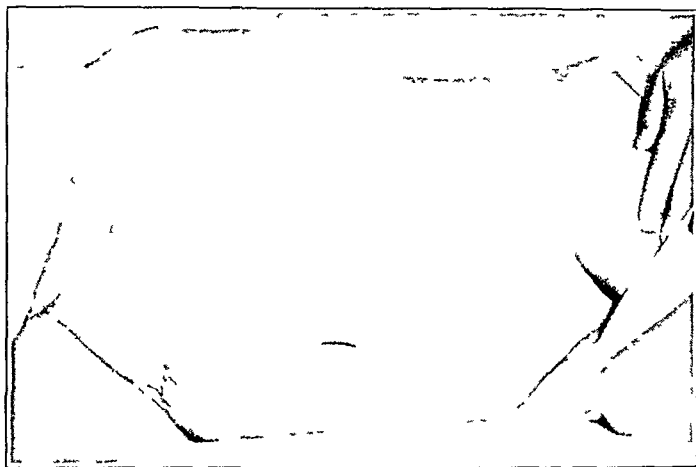


Fig. 3—Tumors on the abdominal skin, a large tumor near the umbilicus

There was a rise in temperature with superficial tenderness of the spleen. A friction rub was heard, and a diagnosis of perisplenitis was made. On October 8 there was extreme nausea, and purpuric spots appeared on the face and neck. On October 10 the patient became comatose. The respiratory rate dropped to 6 per minute, and the pulse was weak and thready. Death occurred on this date.

*Autopsy*—The skin presented the appearance described earlier in the clinical record. The axillary, inguinal and cervical lymph glands were considerably enlarged. Many cutaneous and subcutaneous nodules could be felt, one, for example, measuring 2 cm in diameter, in the right breast, was elevated to about 5 mm above the level of the surrounding skin. Another nodule could be felt to the right of and above the umbilicus. This nodule measured 7 cm in diameter, and when it was sectioned it was found to be about 2 cm in thickness and presented a whitish, translucent surface. The skin had an icteric hue. The abdomen contained an excess of peritoneal fluid, greenish with flecks of fibrin. The liver weighed 1,675 Gm, and had a mottled yellowish color, with greenish irregular, anastomosing striations separating the yellow areas. It was firm. The spleen





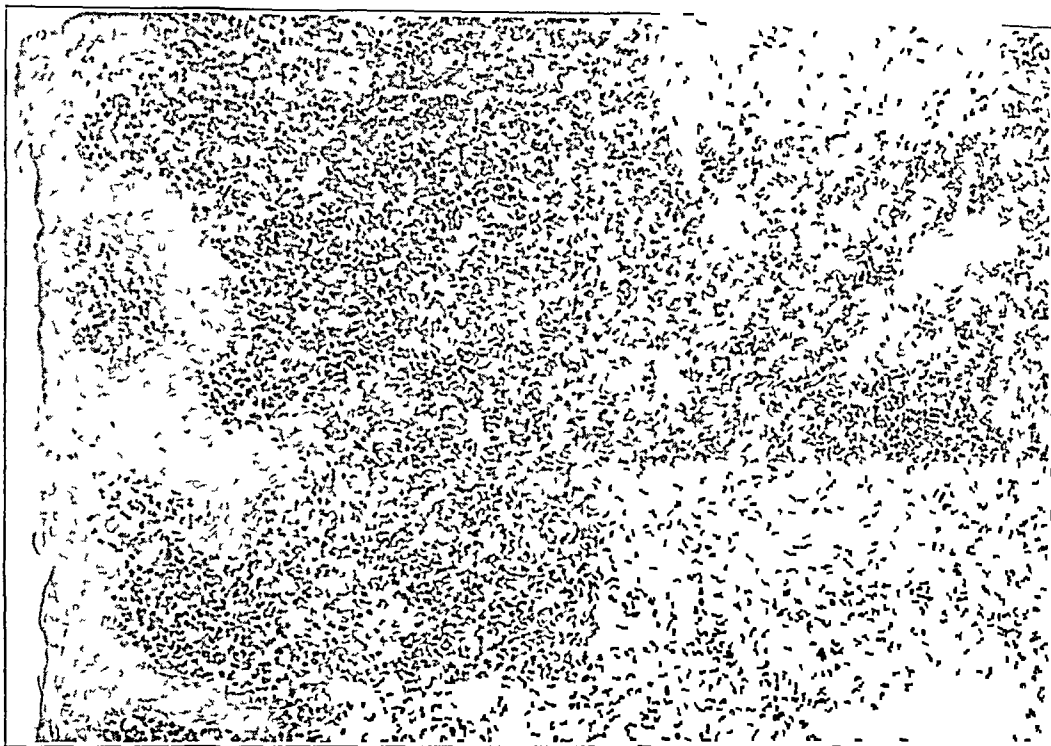


Fig 5—Photomicrograph of skin over a nodule. The entire corium is involved in desquamation and acanthosis. There is hyperplasia of the papillary layer consisting of lymphocytes, lymphoblasts and occasional plasma cells. In some areas these cells have infiltrated into the more superficial portion of the skin. The “free zone” of the cutis is absent.

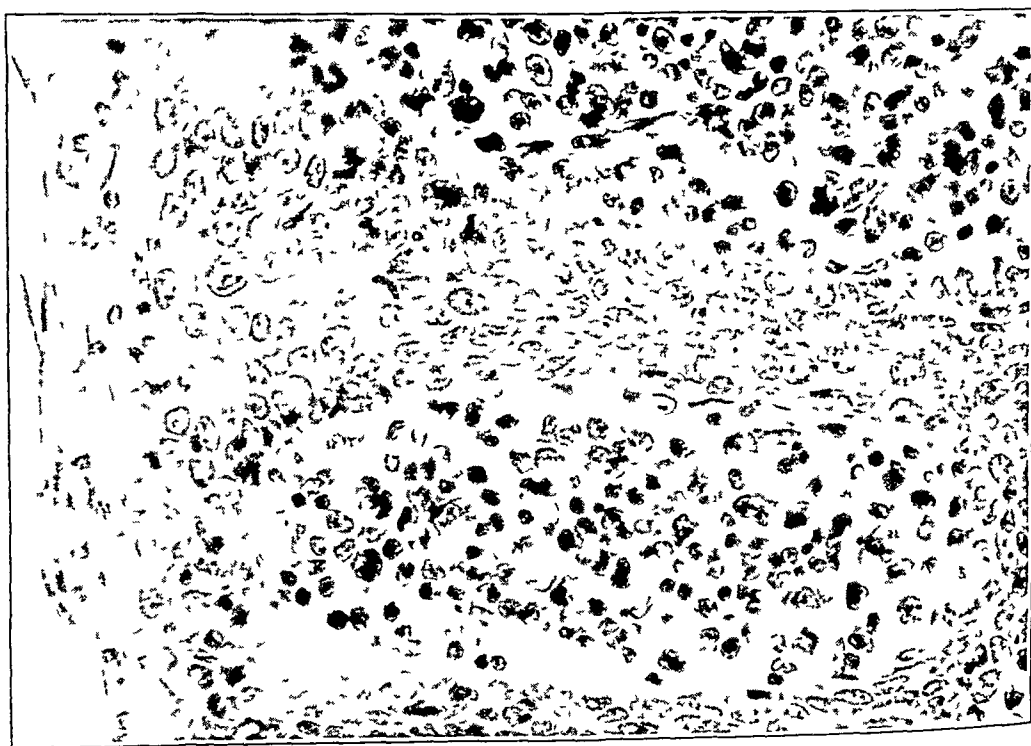


Fig 6—A section of the skin over the edge of a nodule under high power magnification.

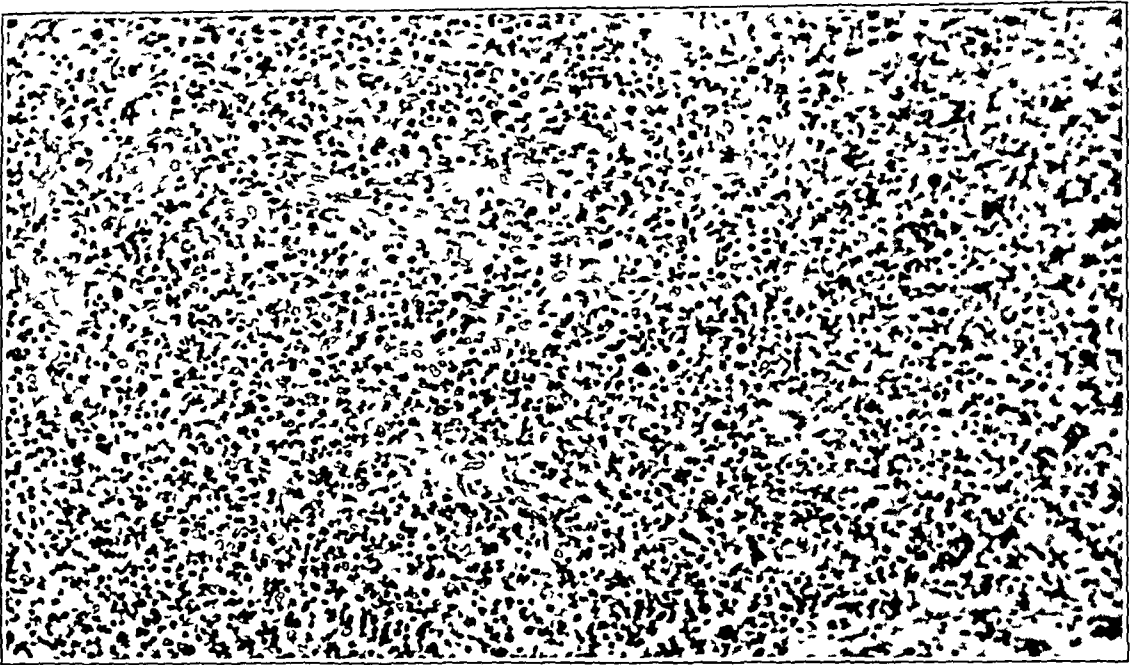


Fig 7—Photomicrograph of a section of a lymph node showing a dense accumulation of lymphocytes in the medullary cords and also large endothelial cells

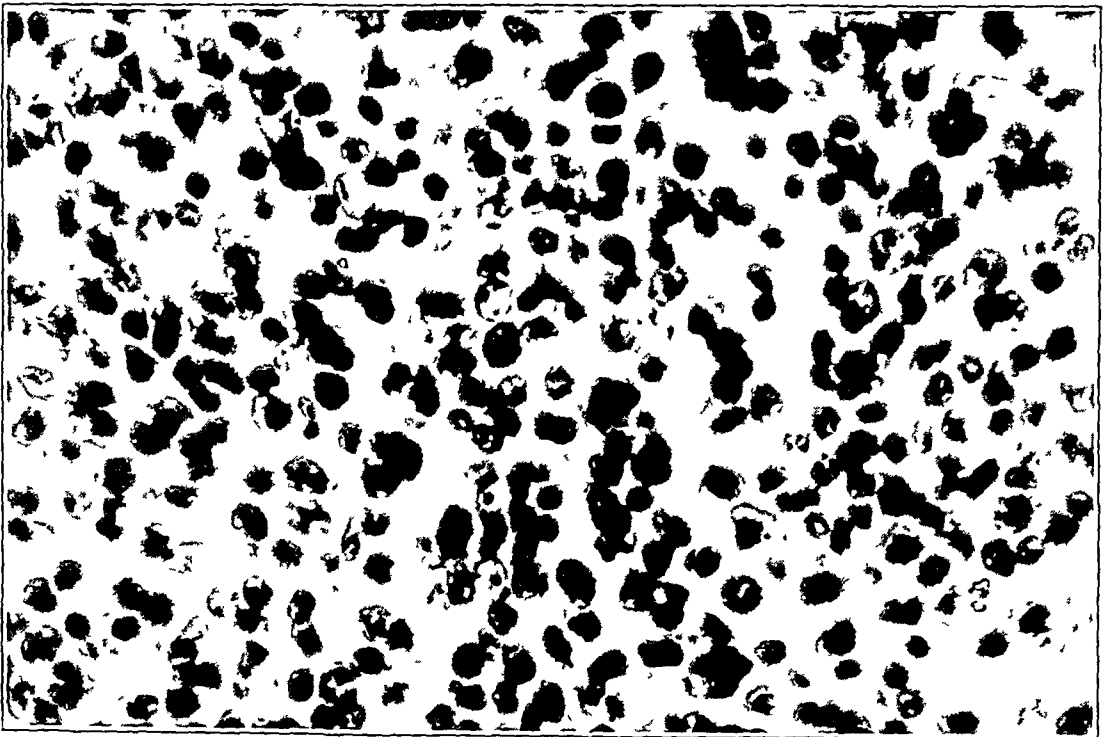


Fig 8—Section of a lymph node under high magnification

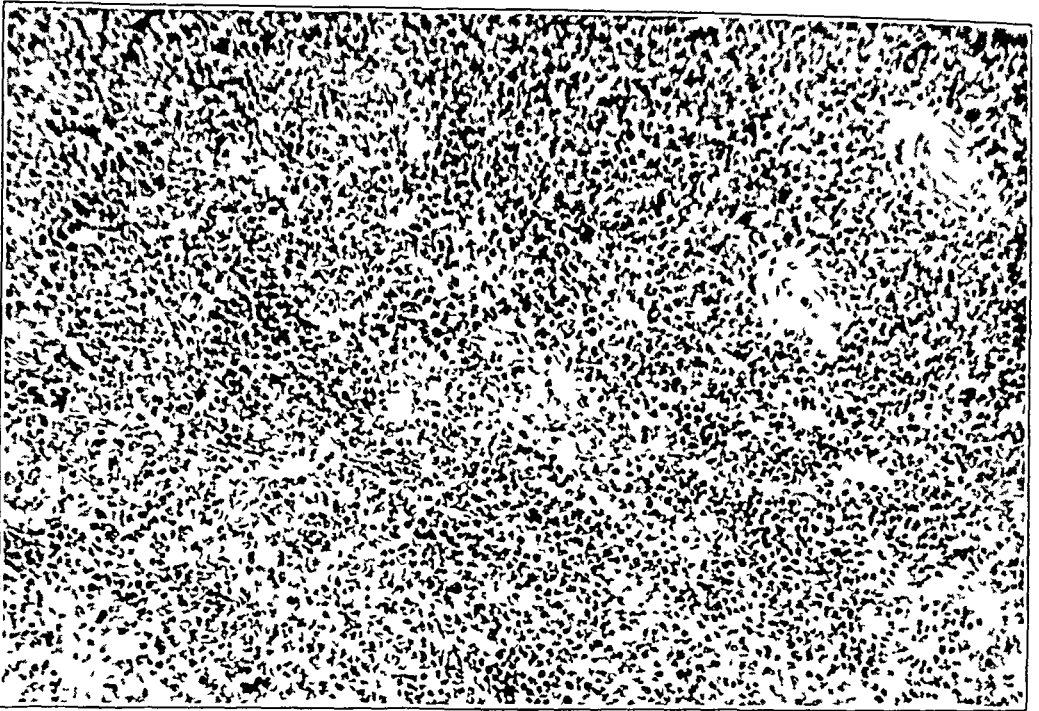


Fig 9—Section of the spleen under low magnification The section shows considerable fibrosis of the pulp A malpighian corpuscle is shown at the right

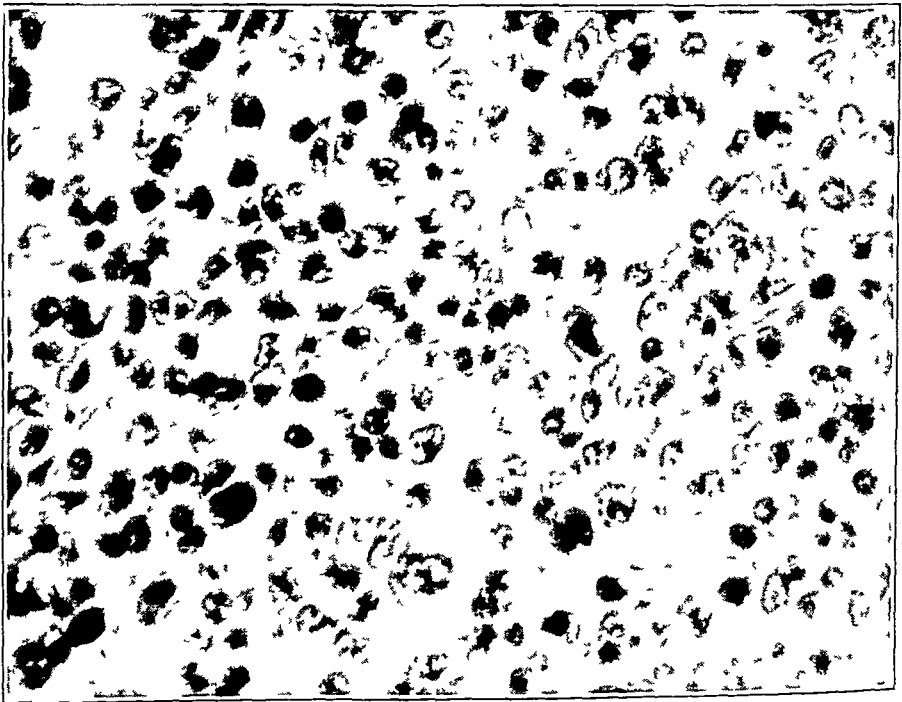


Fig 10—Photomicrograph of tissue from spleen under high magnification This section shows the dense accumulation of lymphocytes of various sizes in the sinuses of the spleen

lation of cells having the same appearance as those described in the nodules in the skin. There was marked endothelial hyperplasia and an occasional large phagocytic cell containing red cells. Fragments of nuclei were seen. Scattered eosinophils were present. The malpighian corpuscles of the spleen were reduced to a small rim around the central artery (figs 9 and 10). The sinuses of the pulp were filled with the cellular infiltrate already described for the other organs. Many areas of fibrosis were present. The amount of blood in the pulp varied considerably in different areas. Eosinophils and plasma cells were numerous. The liver (fig 11) showed marked periportal fatty degeneration and infiltration by round cells. The smears of marrow from the sternum and ribs showed active formation of red and granulocytic cells. The other organs were essentially normal.

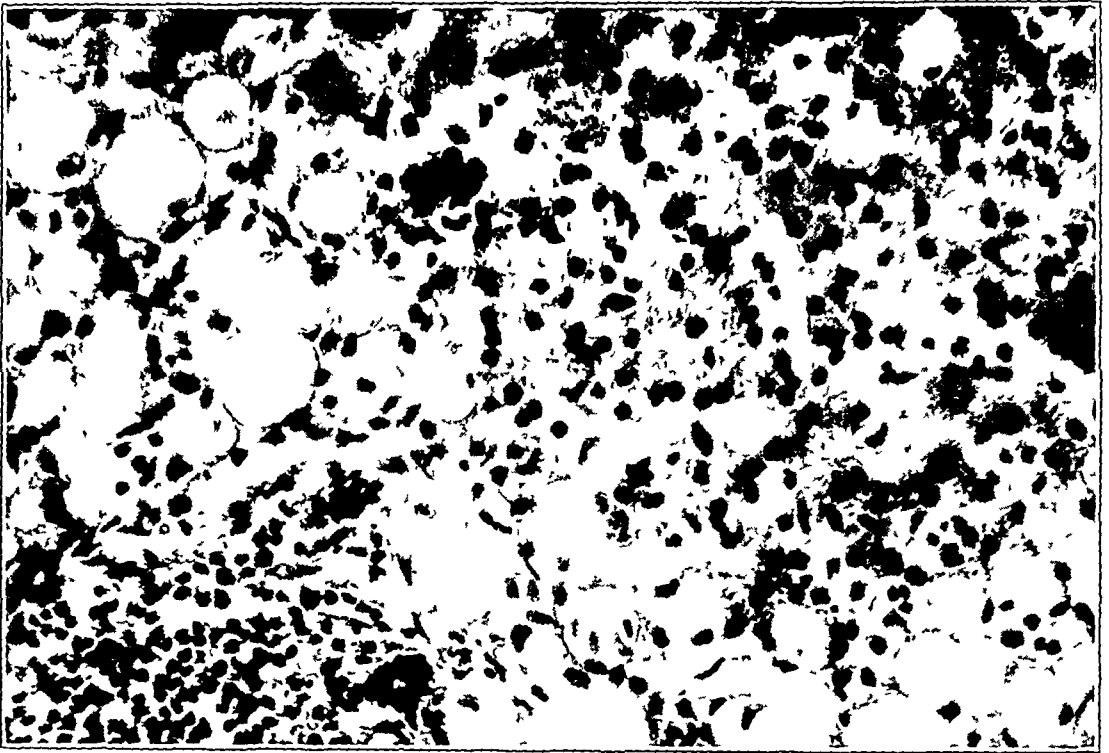


Fig 11—Section from liver showing periportal fatty degeneration and the accumulation of round cells

#### COMMENT

In the lymphoblastomatous group of diseases two types of cutaneous disease are recognized: first, a nonspecific type including exfoliative erythroderma, generalized pruritus, lichenification, urticaria, bullous eruption and prurigo-like nodules, and second, the specific type of true nodular infiltration, which may be well localized or disseminated. It is of particular interest to recognize that these so-called nonspecific lesions do exist. They are of toxic origin and occur in from 15 to 40 per cent of cases, according to Cole. They may, as in the case reported in this paper, precede the formation of cutaneous nodules by months or even years. Chronic exfoliative dermatitis may be only a symptom of some

fatal underlying systemic disease, even in the absence of changes in the glands or blood. Cases exemplifying this fact have been reported by Miller,<sup>6</sup> and Arndt,<sup>7</sup> Doesseker, Breitkopff, Hoffman, Bacher, Saifeld, and others. Nekam in 1899 reported four cases of what he considered to be undoubted leukemic infiltration of the skin, but Whitfield<sup>8</sup> cast some doubt on this diagnosis and stated that the condition is extremely rare. Miller<sup>6</sup> stated that Grosz in 1906 undoubtedly described the first example of a true lymphogranulomatous infiltration of the skin. Since then cases have been reported by Blumsgaard, Sibley, Hirshfeld, Alderson, Fox and others. Miller<sup>6</sup> stated, in a review of the literature, that only a few of these cases are instances of true lymphogranuloma. The others are simply extensions from neighboring glands or deep subcutaneous lesions. In his series of fifty-five cases, collected at the University of California Hospital, only one showed true specific infiltration of the skin. In this case at least one third of the surface of the body was covered with raised, infiltrated plaques at the time of death. The patient was a man, aged 34, with enlarged axillary and inguinal lymph glands and a large spleen. His blood count was 18,000, with 65 per cent polymorphonuclears, 5 per cent eosinophils, 7 per cent lymphocytes and 23 per cent large mononuclear lymphocytes.

Rulison<sup>9</sup> reported a case of Hodgkin's disease of the skin and reviewed the literature, stating that up to 1930 there had been reported only thirty-one accepted cases and that most of these were characterized by the formation of tumors in the skin. He stated that in 10 per cent of all cases of Hodgkin's disease cutaneous manifestations are the first symptoms and are of toxic origin. His patient was a woman aged 38. An erythematous eruption without exfoliation preceded the adenopathy by two months. Biopsy of the skin and glands showed the microscopic appearance typical of Hodgkin's disease in both specimens. The blood count was 11,900, with 62 per cent polymorphonuclears, 1 per cent eosinophils, 6 per cent large lymphocytes and 31 per cent small lymphocytes.

Elsner<sup>3</sup> and Whitfield<sup>8</sup> expressed the belief that multiple cutaneous nodules are not uncommon in this disease. Whitfield examined material taken in two such cases in which late in the disease there was a slow formation of nodules in the skin. They flattened out the epidermis, producing a tense, purplish-red, discolored infiltration. They were firm,

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6 Miller, H. E. Lymphogranulomatosis Cutis. Hodgkin's Disease, *Arch Dermat & Syph* **17** 156 (Feb.) 1928.

7 Arndt, G. *Dermat Ztschr* **18** 1139, 1911.

8 Whitfield, A., quoted in Allbutt, T. C., and Rolleston, H. D. *A System of Medicine by Many Writers*, New York, The Macmillan Company, 1911, vol 9, p 328.

9 Rulison, R. H. Hodgkin's Disease of Skin. Report of Case, *Arch Dermat & Syph* **22** 389 (Sept.) 1930.

and no yellow transparency could be observed on pressing out the blood Whitfield<sup>8</sup> stated that his description tallies closely with the cutaneous symptoms described in true leukemia

Ketron and Gay<sup>10</sup> reported a case of universal lymphatic leukemia of the skin in a man aged 63. Their patient showed the nonspecific type of lesion, with a typical blood count and typical lymphocytic infiltration of the epidermis. This was the sixth case reported up to 1923, the others having been reported by Riehl,<sup>11</sup> Linser,<sup>12</sup> Rodler-Zipkin,<sup>13</sup> Arndt<sup>7</sup> and Bernhardt<sup>14</sup>. Bernhardt's case was the only one in which there were nodules or tumors in the skin. A summary of all the cases reported up to 1923 is given from Ketron and Gay's<sup>10</sup> article (table 2). To these must now be added Keim's<sup>1</sup> case reported in 1924 and Schmidt's<sup>15</sup> case reported in 1931. Ketron and Gay<sup>10</sup> expressed the belief that the apparent rarity of cases reported is due in part to insufficient studies of the blood in cases of universal dermatitis and perhaps also to the fact that many of the cases reported as instances of pseudo-leukemia were really cases of leukemia in a stage of remission.

According to Arndt<sup>2</sup> the typical picture in leukemia cutis is a lymphocytic infiltration with the large lymphocytes and lymphoblasts predominating over the small lymphocytes. The circumscribed lymphadenoses are almost entirely composed of small lymphocytes. When the rash is universal, numerous mitoses are found. Arndt<sup>2</sup> further described a characteristic zone in the papillary layer which is free from infiltration. He stated that in large tumors there may be an absence of hair follicles and sebaceous and sweat glands. Ketron and Gay<sup>10</sup> expressed the belief that the cellular exudate is not confined to any one type of lymphocytic cell but may vary according to the age of the cell and perhaps according to further development in the tissues. Furthermore, it is extremely difficult to differentiate the cells when they are so closely packed together.

In 1931 Schmidt<sup>15</sup> reported a case of leukemia cutis in a child, aged 2 years, who showed numerous flat, button-like lesions in the skin, which were freely movable, painless and the color of a bruise. She died

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10 Ketron, L. W., and Gay, L. N. Universal Lymphatic Leukemia of Skin, *Bull. Johns Hopkins Hosp.* **34**: 404 (Dec.) 1923.

11 Riehl, G. Leukemia Cutis, *Wien klin. Wchnschr.* **6**: 6, 1893.

12 Linser, P. Beiträge zur Frage der Hautveränderungen bei Pseudoleukämie, *Arch. f. Dermat. u. Syph.* **80**: 3, 1906.

13 Rodler-Zipkin, R. Ueber einem Fall von akuter grosszelliger lymphatischer Leukämie mit generalisierter Hauterkrankung, *Virchows Arch. f. path. Anat.* **197**: 135, 1909.

14 Bernhardt, R. Ueber die Leukämie der Haut, *Arch. f. Dermat. u. Syph.* **120**: 17, 1914.

15 Schmidt, F. R. Leukemia Cutis. Report of a Case, *Arch. Dermat. & Syph.* **24**: 587 (Oct.) 1931.

TABLE 2—Summary of Data on Reported Cases of Universal Lymphadenosis of the Skin \*

Author	Sex	Age	Duration	Beginning	Character of Eruption	Glands	Liver and Spleen	Greatest White Cell Count	Percentage of Lymphocytes in Blood	Autopsy Findings	Histologic Appearance of Skin
Riehl <sup>11</sup>	F	57	4 yrs	Eczematous itching patches on back	Generalized reddening and swelling with thickening of skin of face, neck and inguinal regions, surface generally dry with moderate scaling, here and there moist areas	Size of pea to that of apple	Distinctly enlarged	Proportion of white cells to red cells, 1:24		Characteristic changes of lymphatic leukemia	Infiltration of various sized round cells with large nuclei and scant protoplasm, numerous eosinophils
Lisner <sup>12</sup>	M	58	1½ yrs	Vesicular, reddish, itching eruption in bend of joints	Generalized thickening and reddening of skin which was covered with scales, excoriations over buttocks, skin bled easily	Enlarged to size of apple	Enlarged	47,000	94%		Dense infiltration in the cutis composed for the most part of small lymphocytes, a few mast cells, no eosinophils or plasma cells
Rodler Zipf <sup>12</sup>	F	41	3 yrs or more	Itching, reddish patches	Generalized diffuse reddening, scaling and thickening of skin dry and like parchment	Markedly enlarged	Enlarged	41,000	Large 28% Small 15%	Infiltration of liver and spleen with large lymphocytes	Cutis densely infiltrated with large lymphocytes, numerous giant cells, mast cells, a few mast cells, and plasma cells, no eosinophils
Arndt <sup>7</sup>	M	55	8 mos	Severe itching with generalized reddening and swelling of skin	Generalized diffuse reddening and thickening of skin, moderate scaling, moist areas here and there	Enlarged to size of child's fist	Not palpable	500,000	78%	Leukemic changes in internal organs	Dense lymphatic infiltration in cutis with large lymphoblasts and lymphocytes predominating, giant cells present, also a few mast cells and eosinophils
Bernhardt <sup>14</sup>	F	57	2½ yrs	Reddish, scaly itching eruption on scalp	Generalized thickening and reddening of the skin with abundant scale formation, areas of atrophy, nodules and warty formation	Enlarged	Spleen enlarged	51,000	Large 12% Small 72%		Dense infiltration of small lymphocytes in cutis, a few mast and eosinophil cells
Ketron and Gay <sup>10</sup>	M	63	10 mos	Intense itching and reddening of legs	Generalized thickening and reddening of skin, profuse scaling, skin bled easily, warty formation on ankles	Size of English walnut	Spleen enlarged but not palpable	181,000	Large 2% Small 90%		Dense infiltration of cutis by small lymphocytes with moderate number of fixed tissue cells, no eosinophils, numerous groups of plasma cells

\* Taken from Ketron and Gay <sup>10</sup>

within one year from the onset of symptoms. The glands, spleen and liver were not palpable. Nine white blood cell counts were between 3,800 and 20,000, with an average of 9,000, and showed lymphocytosis, with an average of 80 per cent. Many of the lymphoid cells in the smears resembled lymphoblasts. About one third of the lymphoid cells were blastomatous in type.

Sequeira<sup>16</sup> in 1921 reported three cases under the name lymphoblastic erythroderma, which he described as a disease entity apart from mycosis fungoides and leukemia. The condition in his cases was characterized by a specific change in the blood, a leathery, red, exfoliative skin and, in one case, a general adenopathy. The white blood cell counts averaged 9,500, and the differential count showed a reversal of the normal lymphocyte-neutrophil ratio. He did not believe the cases to be instances of true leukemia, because, as he stated, in true leukemia the count is higher and the relative percentage of lymphocytes is greater. In the light of knowledge from more recent articles, it is quite likely that Sequeira's cases might well have been classified as leukemia even in the absence of high white blood cell counts. Furthermore, in Sequeira's<sup>16</sup> opinion most cutaneous infiltrations occur in the myeloid type of leukemia. Elsner,<sup>3</sup> Warthin<sup>5</sup> and Longcope, on the other hand, stated that cutaneous nodules are relatively frequent in both acute and chronic lymphatic leukemia. Montgomery<sup>17</sup> also recognized dense infiltration of the skin both in lymphatic and in myelogenous leukemia. Arndt<sup>2</sup> contended that up to 1914 myeloid leukemia with a diffuse universal participation of the skin with typical myeloid tissue had not been observed, and certainly circumscribed involvement of the skin is extremely rare. Arzt<sup>18</sup> recognized a predilection of the lymphocytic tumors for the nose, cheeks, eyelids, lips, chin, ears, ear lobes and glabella, producing a facies leontina such as lepers show, although the tumors do occur also on the breasts, abdomen, scrotum and other parts of the body. Schmidt<sup>15</sup> stated that there have been only a few reports in the literature of lymphatic leukemia in which the diagnosis of true leukemia cutis has been supported by histologic evidence. Keim<sup>1</sup> said that universal leukemia cutis with general hyperplastic proliferation does not occur in myeloid leukemia, and so the term refers to a universal lymphadenosis of the skin occurring in the course of lymphatic leukemia. His patient showed an exfoliative dermatitis, papillomatous

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16 Sequeira, J. H., and Panton, P. N. Lymphoblastic Erythrodermia, *Brit J Dermat* **33** 391 (Dec.) 1921.

17 Montgomery, H. Exfoliative Dermatoses and Malignant Erythroderma. Value and Limitations of Histopathologic Studies, *Arch Dermat & Syph* **27** 253 (Feb.) 1933.

18 Arzt, L. Leukämische Erkrankungen der Haut, *Wien klin Wchnschr* **46** 1125 (Sept. 15) 1933.



growths on the extremities, general adenopathy, a palpable liver and spleen and a blood count of 30,000, with a differential count of 28.5 per cent polymorphonuclears, 0.5 per cent eosinophils, 56.5 per cent small lymphocytes, 10 per cent large lymphocytes, and 0.5 per cent transitionals. The count later rose to 85,000, with predominance of a white cell which was a medium-sized lymphocyte with a small amount of fragile cytoplasm. In type it was about midway between the ordinary large and small lymphocytes of normal blood. The diagnosis was supported by complete autopsy.

#### CONCLUSION

Under the grouping of lymphoblastoma cutis are included four diseases—leukemia, Hodgkin's disease, lymphosarcoma and mycosis fungoides. They may or may not be accompanied by changes in the blood and internal organs, but all may affect the skin by actual invasion of the corium. They resemble each other so closely that differentiation is often impossible. Generalized exfoliative dermatitis is a common precursor, often preceding the formation of specific cutaneous tumors by several years. Complete remission may occur but in all cases the disease is eventually fatal.

A case of seven years' duration has been described. There were early exfoliative dermatitis and enlargement of the lymph glands and the changes of the blood typical of lymphatic leukemia. Early biopsy confirmed this diagnosis. The patient had a remission and later presented tumors of the skin and enlargement of the spleen. The total white blood cell count remained relatively low and showed the same types of cells originally observed. There was a widespread exfoliative dermatitis, the etiology of which is always obscure and which shows the necessity of careful hematologic and histopathologic study. A survey of the literature reveals a necessarily widespread divergence of opinion as to the typical pictures of the various entities of this group.

# ARRHENOBLASTOMA A SPECIAL TYPE OF TERATOMA

REPORT OF A CASE

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Since Pick,<sup>1</sup> in 1905, first described a tumor of the ovary closely resembling the seminiferous tubules of the testis, others, usually of more atypical structure, have been described. These growths are made up of apparently masculine tissue and influence the secondary sex characteristics in a masculine direction, but, strangely, those with the least microscopic resemblance to testis show the greatest masculinizing effect. The tumor is mildly malignant, and direct extension occurs, although true metastasis has not been reported. Originally called adenoma testiculare ovarii, it has more recently been designated arrhenoblastoma, from the Greek *arrhen*, meaning male.

The arrhenoblastoma was thought by Meyer<sup>2</sup> to arise from certain embryonic remains incorporated in the ovarian medulla, and he considered the microscopic appearance of the tissue to be characteristic. Novak and Long<sup>3</sup> recently discussed this type of tumor together with the more frequent feminizing granulosa cell tumor, they found twenty-eight cases of arrhenoblastoma of all grades of embryonic differentiation reported in the literature. Only three were reported in the American literature, and Novak and Long reported another after examination of their old pathologic material. Klock, in his discussion of the paper by Novak and Long, suggested that the tumor might be a teratoma, consisting chiefly or entirely of testicular tissue rather than the more usual elements.

I am reporting a case in this group, with evidence that the tumor was a teratoma.

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1 Pick, L. Ueber Adenome der mannlichen und weiblichen Keimdruse bei Hermaphroditismus verus und spurius. Nebst Bemerkungen uber das endometrium-ahnliche Adenom am inneren weiblichen Gentale, Berl klin Wchnschr **17** 502, 1905, quoted by Novak and Long<sup>3</sup>

2 Meyer, Robert. Pathology of Some Special Ovarian Tumors and Their Relation to Sex Characteristics, Am J Obst & Gynec **22** 697, 1931

3 Novak, E., and Long, J. H. Ovarian Tumors Associated with Secondary Sex Changes. Granulosa Cell Carcinoma and Arrhenoblastoma, J A M A **101** 1057 (Sept 30) 1933

## REPORT OF CASE

*History and Course*—Mrs T W S, a 32 year old housewife, was first seen on Oct 3, 1933, complaining of hoarseness, an abdominal tumor and an unusual growth of body and facial hair. Her father had died of carcinoma of the stomach. There had been no endocrine disorder and no known developmental anomaly in her family.

In the past, the patient had had no significant illness. She was a rather feminine type of woman, with a rounded body and a good complexion, her voice

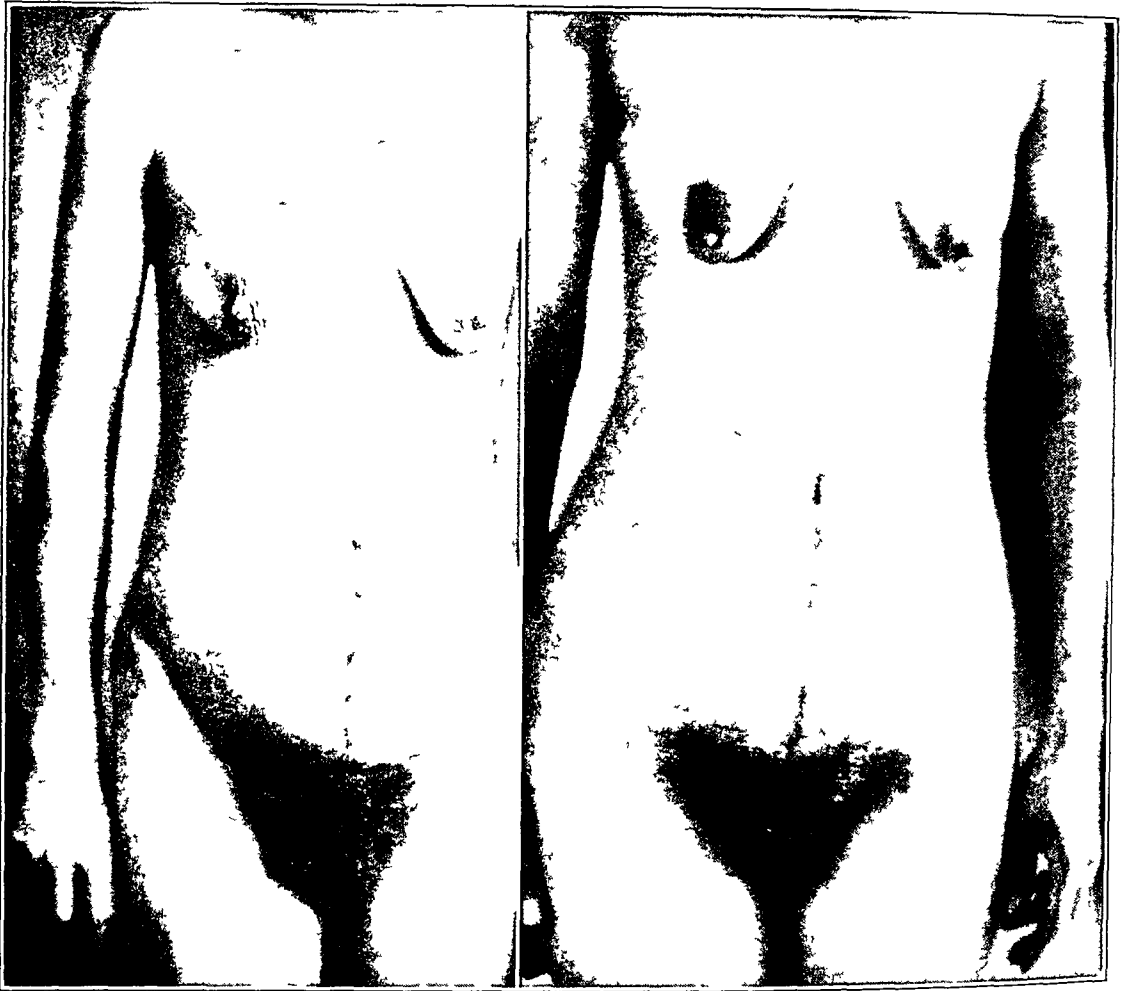


Fig 1—The figure on the left shows the patient on Oct 18, 1933, before operation, with profuse masculine pubic hair and flat breasts, and that on the right, made on May 9, 1934, six months after operation, shows the pubic hair to be of feminine type and the breasts fuller. The operative scar can be seen.

was high-pitched, and the distribution of body hair was of feminine type. The menses began at 13 years, were rather profuse, lasted five days and recurred regularly every twenty-eight days. There had been seven pregnancies, the fourth and the sixth ending in miscarriage. After the birth of the first three children and after both miscarriages, the menses returned in the first month post partum. After the birth of the fourth child, the patient did not menstruate until the fifth month.

After the birth of her last child, in March 1930, the patient menstruated but twice, in the fourth and sixth months post partum. She felt tired and weak, and she could feel a mass the size of an egg in the abdomen. There was no other specific complaint. In January 1932 she began to be hoarse, particularly after talking for a long time. The body hair gradually became heavier and darker, and she began to shave, occasionally at first but finally every day. The mass slowly increased to the size of a large grapefruit, but at no time was there abdominal discomfort. In the three years the patient had lost about 15 pounds (6.8 Kg). There was no definite change in her libido. The amenorrhea continued.



Fig 2—The figure on the left shows the patient on Oct 18, 1933, before operation, four days after shaving. The beard and prominent thyroid cartilage can be seen. The figure on the right shows the patient on May 9, 1934, six months after operation, ten days after shaving. The beard cannot be seen and the face is tanner. The thyroid cartilage is still prominent.

Physical examination in October 1933 revealed the patient to be slight, with little body fat and a somewhat boyish figure. The voice was husky and changeable, like that of a boy at the age of puberty. The body hair was of masculine type, with a fairly heavy beard and coarse black hair on the arms and legs, in the axillae, around the nipples and on the abdomen. The area of pubic hair had a convex upper border and extended up to the umbilicus. The thyroid cartilage was unusually prominent. The breasts were flaccid and contained little fat. In the midline of the lower portion of the abdomen there was an irregularly spherical, firm, nontender mass about 15 cm in diameter. It could be moved freely into

either flank without causing discomfort, when pulled into the upper portion of the abdomen it caused a "drawing" sensation in the suprapubic region. It could not be felt on pelvic examination. The uterus was in first degree retroversion, and there seemed to be no connection between it and the abdominal mass. The clitoris, measuring 3 cm long and 1 cm in diameter, was enlarged and erectile. Physical examination revealed no other abnormality.

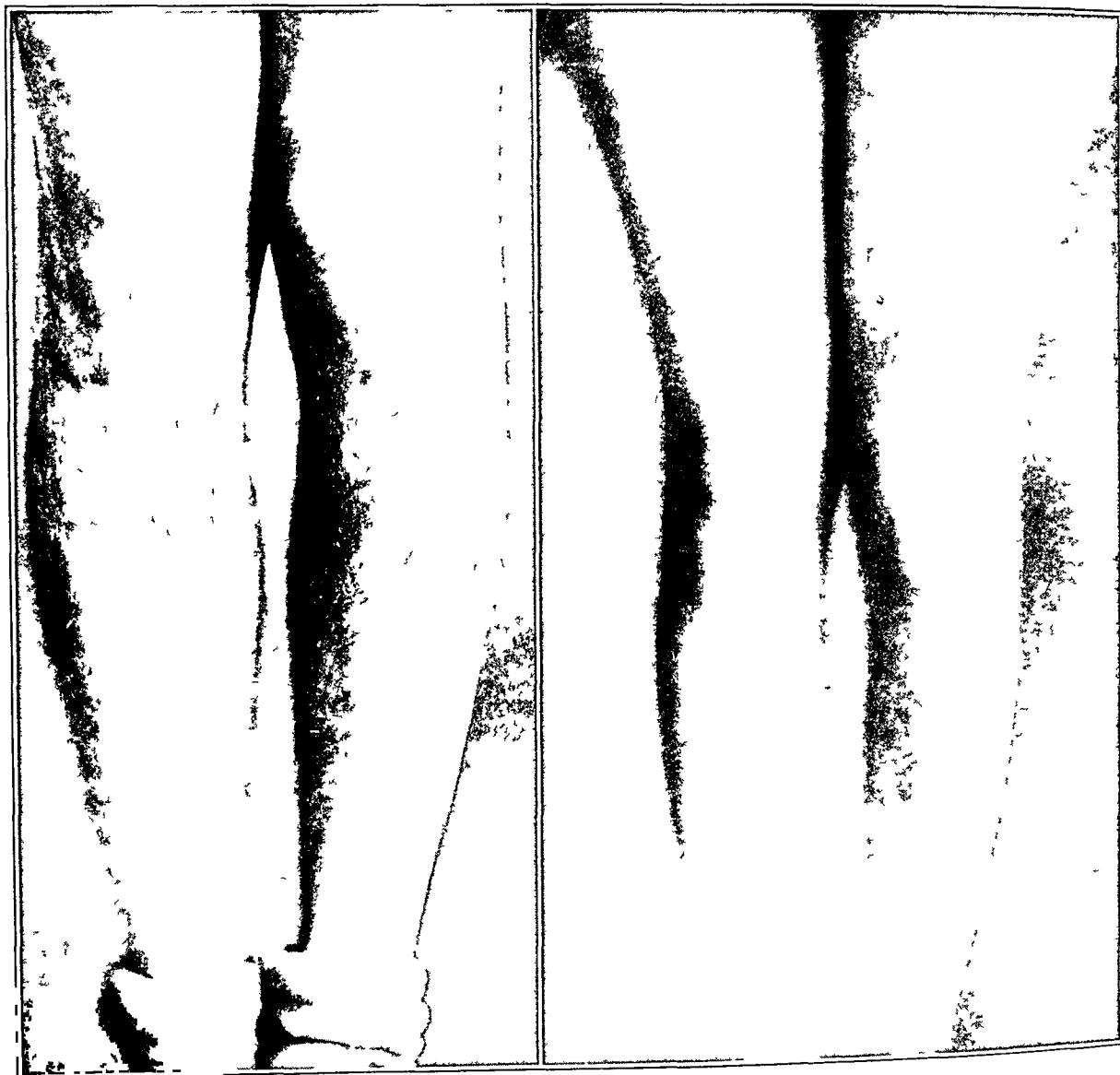


Fig 3—The figure on the left shows the patient on Oct 18, 1933, before operation, with profuse hair on the legs, and that on the right, made on May 9, 1934, six months after operation, shows no hair.

There was moderate secondary anemia. The basal metabolism was 36 and 41 per cent above the average on two occasions. Roentgenograms of the skull and chest showed no evidence of disease.

At operation (by Dr S L Ledbetter Jr) on Oct 19, 1933, a tumor the size of a large grapefruit, apparently of the right ovary, was found. Adherent to its

surface was a tab of omentum. The tumor was attached to the right fallopian tube by a small ovarian pedicle, elsewhere it was unattached. There was no evidence of extension other than that in the adherent omentum. On the left side were a nodule 8 mm in diameter in the tube and two small masses, the larger, 4 cm in diameter, connected with the ovary by a cordlike band 2 cm long. The other was connected to this one by a cord and also to the tube by a small cordlike band. The left ovary was of normal size, hard, pale and sclerotic and contained no visible follicles. The uterus was of normal size. The large tumor of the right ovary was removed with the tube and the omental attachment, and the left tube with the small nodule, and the two small masses were removed. The left ovary and the uterus were left in place.

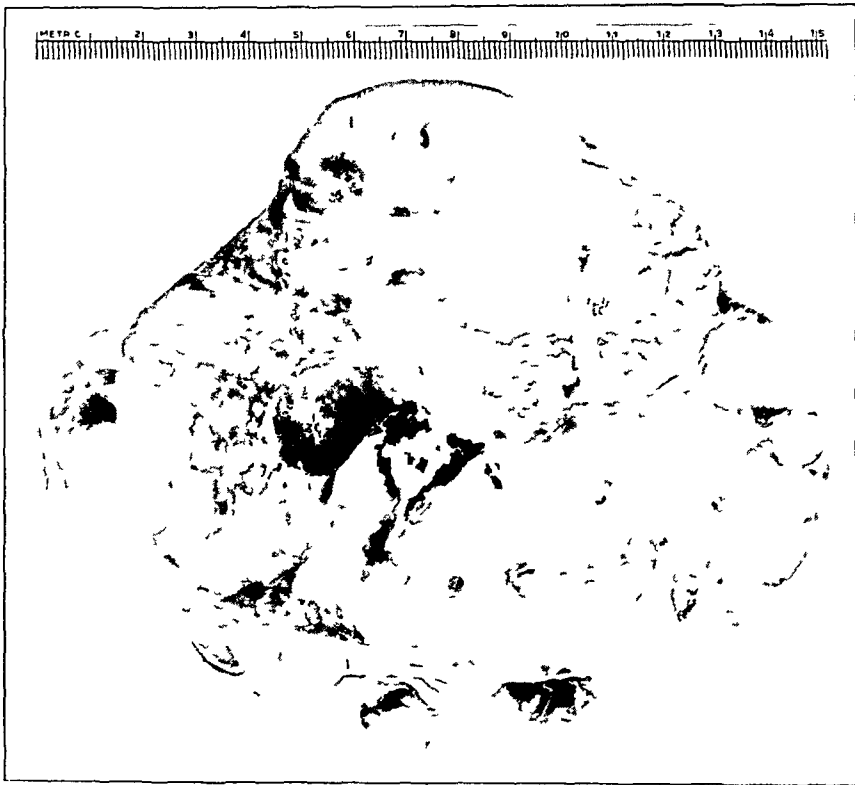


Fig 4—The bisected tumor. The oviduct is suspended below. Surviving ovarian tissue can be seen along the lower left-hand margin of the mass.

The postoperative course was marked by a gradual return of feminine characteristics. On about the tenth day the patient's voice was higher-pitched, and talking was easier. Though it becomes husky on occasions, her voice has continued to be better. On the twenty-ninth postoperative day a normal menstrual period began. Since then the menses have been on rare occasions slightly irregular and somewhat less profuse than formerly but otherwise normal. There was little change in the body hair until late in February 1934, four months after, when it was noticeably less heavy and was falling out in large quantities. In April, the sixth postoperative month, the pubic hair was of feminine distribution, hair on the abdomen and chest had disappeared, the amount of hair on the arms and legs was less, and a week after shaving the beard was scarcely noticeable. At this time the skin was more delicate, the face and figure were somewhat rounder and the breasts were fuller. The thyroid cartilage was still prominent. The clitoris had

become about one third its preoperative size, and the uterus was in a normal anterior position. The basal metabolism had fallen to normal after remaining persistently in the neighborhood of 20 per cent above that figure for five months. The right kidney was palpable for the first time. There were no symptoms referable to it. At no time has there been elevation of the pulse rate, sweating or other evidence of thyroid disease. A year after operation the patient continued to improve, and there was no evidence of recurrence of the tumor.

*Pathologic Examination* (From the Report of Dr. George S. Graham)—The tissue was fixed in Zenker's fluid, Orth's fluid and solution of formaldehyde. Paraffin sections were stained with hematoxylin and eosin and iron and hematoxylin and according to Mallory's eosin and methylene blue, phosphotungstic acid and hematoxylin and aniline blue methods for staining connective tissue.

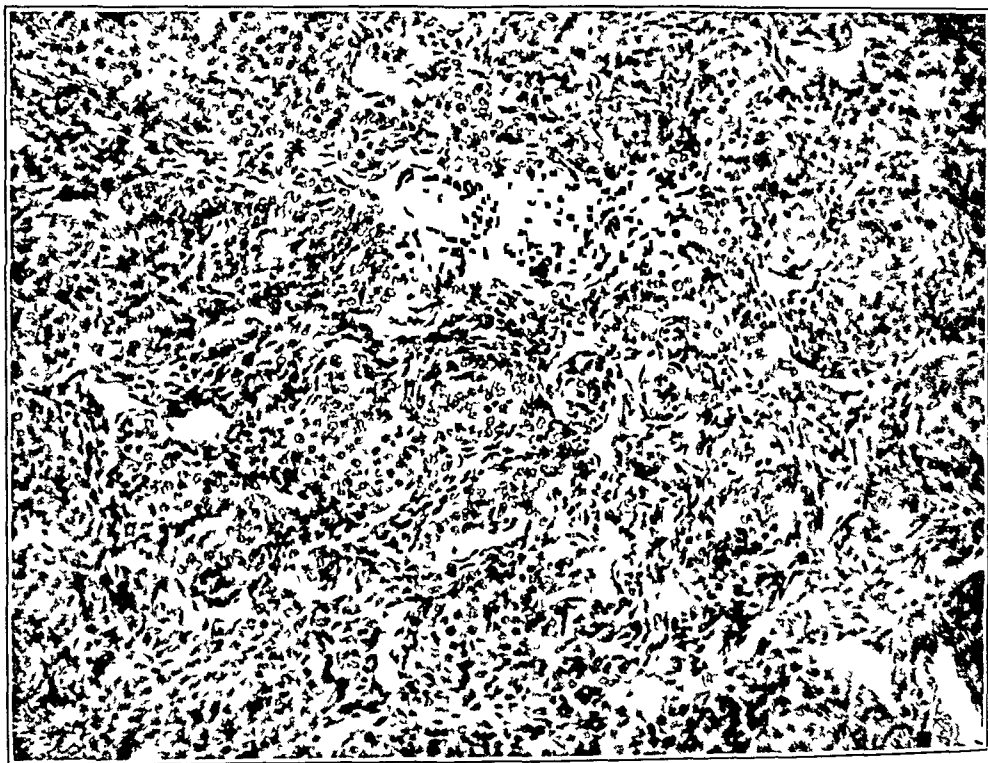


Fig. 5—A typical low power magnification of a denser portion of the ovarian tumor,  $\times 150$ .

Scarlet red was applied to frozen sections and to heavily chromated material fixed in solution of formaldehyde (method of Ciaccio).

The main specimen (fig. 4) was an irregularly ovoid mass, with a smooth opaque capsule of ovarian type. It measured 17 cm. in greatest diameter and weighed 930 Gm. At the broader end was an adherent fragment of omentum. Suspended along one side was an oviduct, free from gross lesions. A small nodulation with a furrowed surface, which on section presented the characteristics of ovarian tissue, projected from the mass alongside the ligament to the tube. An opaque white membrane outlined a cyst about 1 cm. in diameter. The remainder of the mass consisted of soft opaque yellow tissue with an occasional admixture of grayish-white tissue, occasionally translucent and moist. There were scattered hemorrhagic foci. Thin septums sometimes divided the mass into lobular fields.

Beneath the omental adhesion a wide area of firm yellow necrotic tissue extended deeply into the mass, and there were frequent smaller areas of necrosis. At one place there was a cyst 6 cm in diameter. Its lining wall was in part smooth and in part covered by closely placed translucent secondary cysts.

The tumor tissue was made up chiefly of cells of two morphologic types, one rounded or polygonal and the other fusiform (figs 5, 6 and 7). Transitional examples suggested, however, that these were phases of a single basic cell. In the fusiform type the nucleus was elongated and the cytoplasm scanty. It often resembled a fibroblast. The polygonal cell was larger, with a sharply outlined cell body. The rounded nucleus contained coarse chromatin particles and a prominent nucleolus. Characteristically, the delicately reticulated cytoplasm was abundant, with a central, more compact, finely granular portion and a peripheral paler

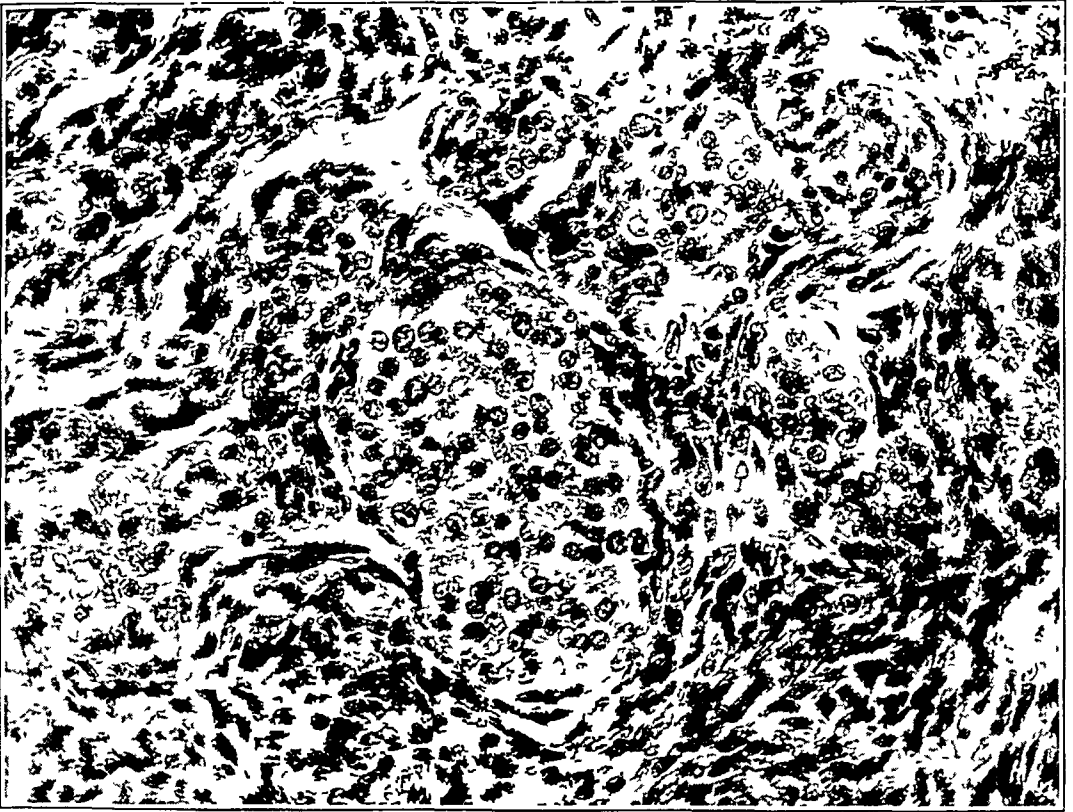


Fig 6—A high power magnification, showing the arrangement of the two cell types observed in the tumor and the intimate relationship of the large cell clumps to the plexiform sinusoidal blood vessels,  $\times 300$

zone of attenuated or vacuolated structure. In some cells there were coarse granulations and irregular or elongated particles of small size, the exact nature of which could not be made out. Frequent inclusion bodies appeared as small eosin-stained, occasionally rather refractile, globules. Furthering the suggestion of the glandular nature of the cell was its arrangement in clumps or columns, outlined by a plexiform arrangement of thin-walled blood vessels. In areas of looser structure the polygonal cells were occasionally present alone. In more compact fields the peripheral cells of the columns often flattened out into a capsular layer of fusiform elements. Again, the fusiform cells predominated, and rarely they completely replaced the other type over a limited area. Sharpest contrast was afforded when islands of large, coarsely granular cells were isolated



in the more compact areas (fig 7) Mitotic figures were numerous but most common in the fusiform cells There were frequent necrotic areas, some of them hemorrhagic In many fields, especially at the margins of necrotic foci, the tumor cells were fewer and appeared as sharply outlined anastomosing columns, from one to several units wide, embedded in a highly vascular collagenous stroma of varying density The columns were widely separated in some places, and the fibrillar stroma was often infiltrated by a fluid material containing many fine hyaline eosin-staining droplets The tumor cells of the columns were of the rounded type and varied considerably in size and cytoplasmic contents

There was a patchy distribution of fat throughout the tumor It occurred within the cytoplasm of the tumor cells, almost always in the rounded or polygonal type (fig 8) In the more compact fields there was little fat, but it became

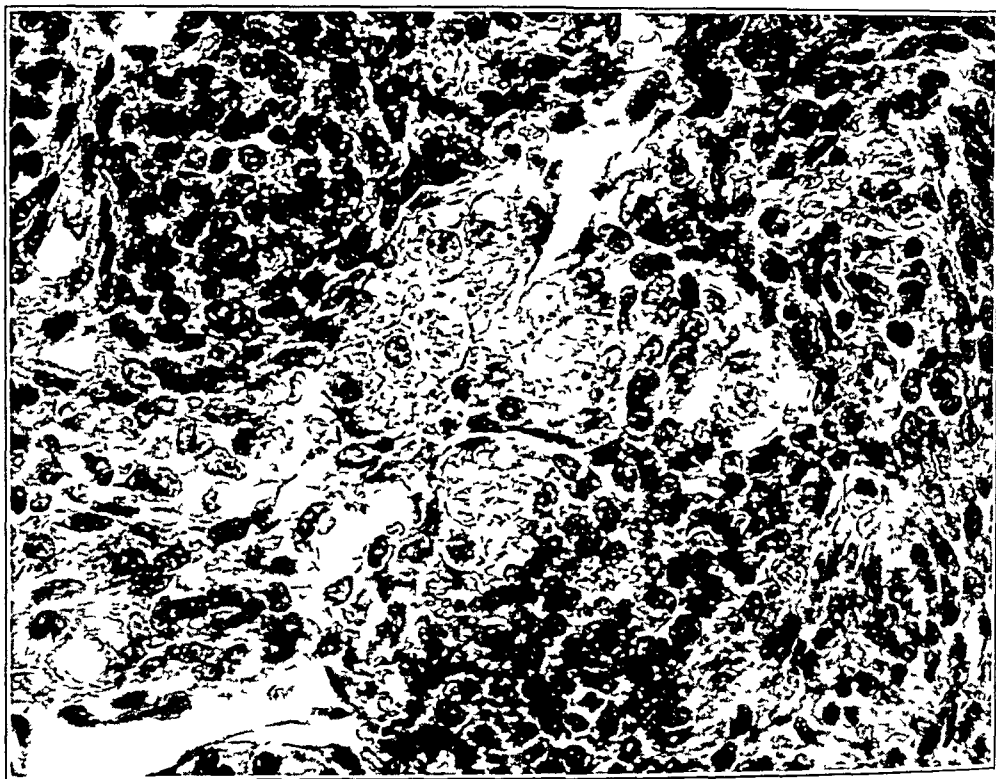


Fig 7—A clump of large cells of the tumor, showing more clearly their gland-like structure and arrangement,  $\times 300$

more common in the looser areas, where in some places most of the cells were thickly dotted with it The fat particles exhibited a peculiar morphologic picture For the most part they appeared as a thin crescent partially outlining a vacuole or globule of unstained material or formed a delicate circlet, crescentically thickened in from a third to a half of its circumference, completely enclosing such a body Some appeared as the usual solid globules, but this may have been due to the angle from which they were observed Most of the bodies were small, and many of them were crowded into the cytoplasmic substance of single tumor cells, but occasional bodies were double or triple the average size The larger bodies, like the smaller circular ones, appeared as signet-rings or hollow spheres They were sometimes present within cells undergoing mitotic division The appearance

was the same in a material fixed in a solution of formaldehyde, whether in frozen sections or in paraffin sections of chromated blocks

The large cyst lying within the tumor was lined by a single layer of columnar epithelium with mucus-producing cells (fig 9) Typical goblet cells were present The epithelium was supported on a shallow zone of loose stroma containing many small cysts Their lining epithelium was sometimes mucus-producing, in some instances free from mucus and in occasional cases flattened The tumor cells at times infiltrated the stroma between the cysts

The left oviduct was 7.5 cm long and 0.8 cm in maximum diameter At the ampulla there was a serous cyst 0.2 cm in diameter lined with ciliated columnar epithelium Within the wall of the tube was a firm, yellowish-white nodule,

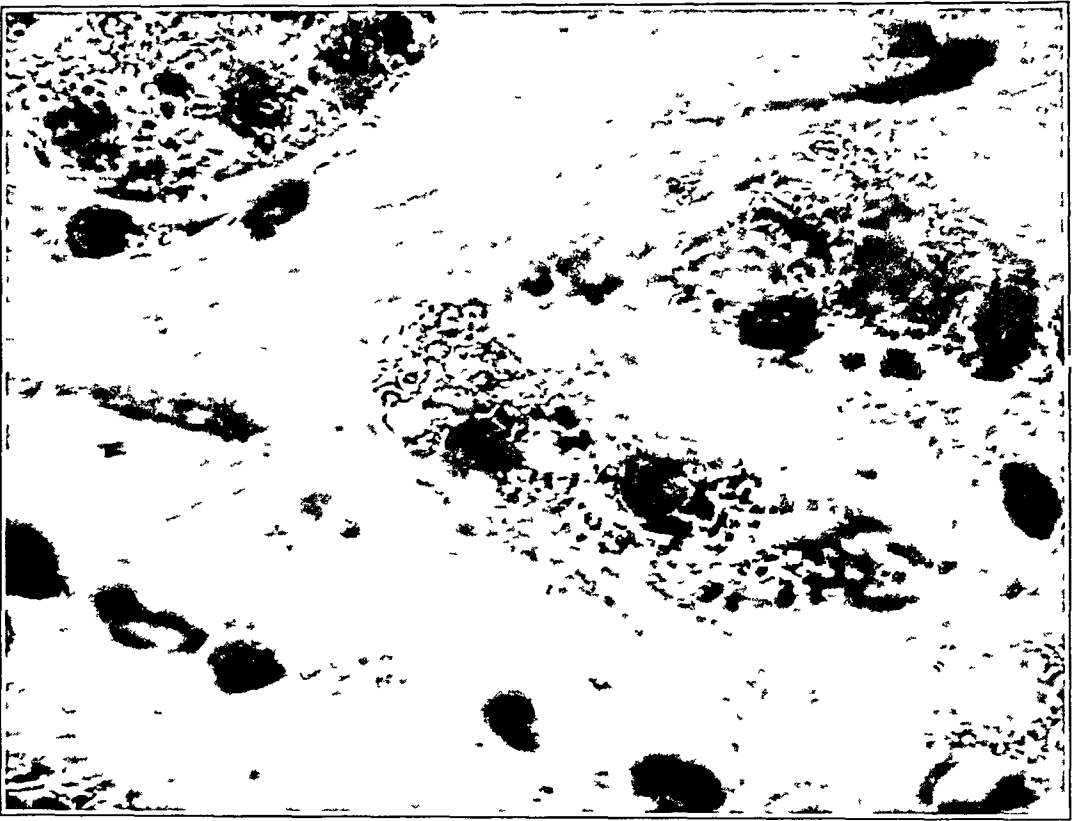


Fig 8—Tumor cells from a looser area cut by frozen section and stained with scarlet red and hematoxylin The cytoplasm is crowded with refractile globular bodies outlined by crescentic or signet-ring fat particles that appear black in the photograph,  $\times 700$

0.6 cm in diameter (fig 10) It consisted in a rich plexus of narrow channels supported in a mesh of fibrous tissue and lined usually by a single layer of flattened cells Rarely these cells became higher or even columnar and definitely epithelial The nodule filled the whole thickness of the wall of the tube on one side It bulged into the tubal lumen, where at its summit the epithelium lining the tube appeared to be in direct continuity with that lining the channels of the tumor There was an occasional suggestion of a similar continuity with the serosal cells covering the tube The sections of the mass presented a picture typical of the rete testis (fig 11)



Fig 9—Lining membrane of the large tumor cyst The single layer of epithelium produces short tubules lined by typical goblet cells This section was taken from the margin of one of the smaller cysts Its epithelial lining bears no resemblance to that of the larger cyst and was not mucus-producing,  $\times 160$



Fig 10—The tumor of rete tissue in the oviduct wall,  $\times 10$

Attached to the outer half of the left tube by two threadlike cords was a firm, grayish-white hour-glass body, with a slightly furrowed surface, 4 cm in length and 2.2 cm in greatest diameter. It consisted largely of extremely dense acellular fibrous tissue. At its surface, however, was a layer of typical ovarian stroma in which were occasional corpora fibrotica. At its center was a narrow cleft lined with a wrinkled membrane colored a slight brownish yellow by many large cells laden with a brown iron-containing pigment. The other mass, described in the

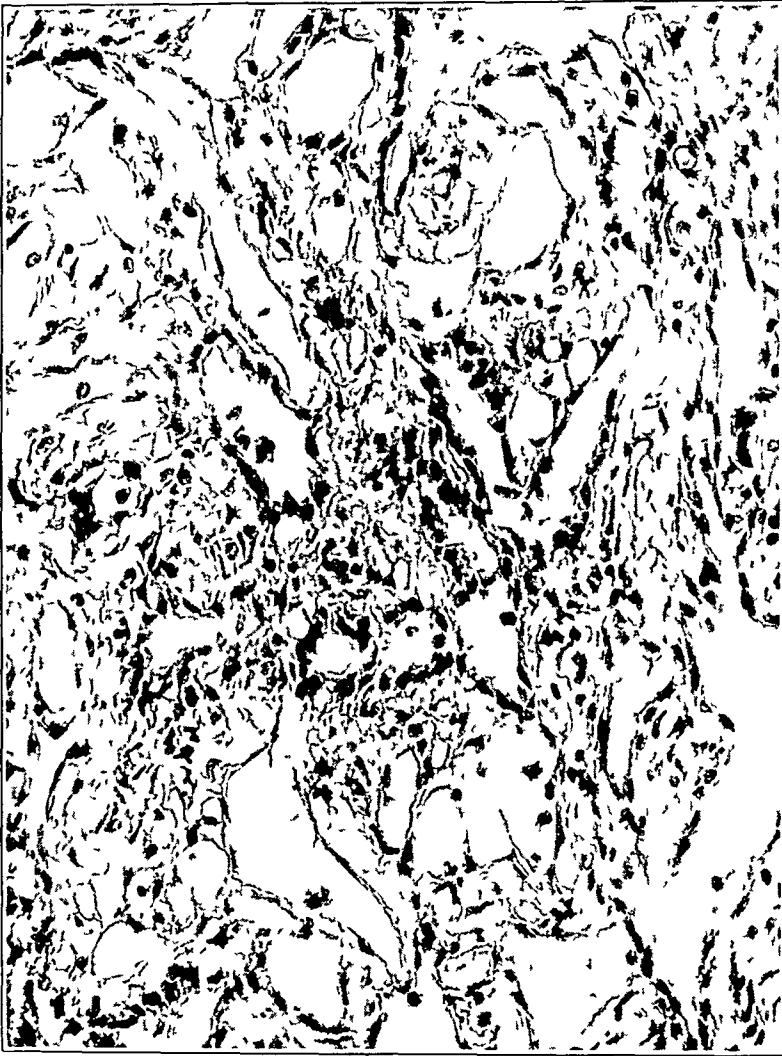


Fig 11—A high power magnification of rete tissue from the wall of the oviduct,  $\times 300$

surgical report, attached to the one just described and to the ovary, was accidentally destroyed.

#### COMMENT

The secondary sexual characteristics of the woman, originally feminine, changed materially in the course of three years. They went beyond the commoner intersexual stage to one definitely masculine. Then, after removal of the tumor, the feminine characteristics returned to a partial degree, and after one year there has been no recurrence.

of the tumor or return of the male characteristics. The mass was ovarian in origin, as shown by its location and by the ovarian stroma found on a part of its periphery. The return of feminine characteristics and particularly the continued normal menstruation after the operation are indicative of a normal function of the remaining gonadal tissue. There was no definite clinical evidence for incriminating any of the endocrine organs other than the ovary. It seems definite, then, that the tumor of the ovary was responsible for the changes noted.

The tumor consisted, probably, of testicular tissue. There was cord formation but no attempt at the construction of tubules or acini, nor was there any spermatogenesis. The chief cells were of two types. One was often noted in groups, with a relation to blood vessels suggestive of endocrine structures in general (figs 6 and 7). This cell exhibited many of the structural characteristics of the testicular interstitial cell of Leydig, especially the peculiar distribution of fat (fig 8) described by Wagner,<sup>4</sup> Whitehead<sup>5</sup> and Winwarter.<sup>6</sup> It did not show the pigment common in the Leydig cell noted in man or the crystalloids of Reinke,<sup>7</sup> which may or may not be present in man. It did not suggest any other normal cell. The second type of cell was fusiform, suggestive of embryonic fibrous tissue, with some evidence of change into the former type. It may have represented the mesodermal tissue from which the interstitial cell is said to arise. If one accepts the contention that the Leydig cell elaborates the male hormone, the clinical course offers confirming evidence which warrants the assumption that these are testicular interstitial cells in varying degrees of development. The microscopic picture, on the whole, was highly suggestive of arrhenoblastoma as it has been described, and the clinical course was so typical that a diagnosis was made before operation. It seems probable, then, that the tumor from my patient falls into the group of arrhenoblastomas and consists chiefly of testicular interstitial cells.

It has been suggested that the arrhenoblastoma is but a special form of teratoma. Ewing<sup>8</sup> mentioned teratomas consisting entirely of thyroid tissue but did not mention such tumors containing gonadal structures. Such a classification would depend on finding in the tumor

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4 Wagner, K. Zur Zytologie der Zwischenzellen des Hodens, *Anat Anz* **56** 559, 1922.

5 Whitehead, R. H. Chemical Nature of Certain Granules in the Interstitial Cells of the Testis, *Am J Anat* **14** 63, 1912.

6 Winwarter, H. Observations cytologiques sur les cellules interstitielles du testicule humain, *Anat Anz* **41** 309, 1912.

7 Rasmussen, A. T. Interstitial Cells of the Testis, in Cowdry, E. V. *Special Cytology*, New York, Paul B. Hoeber, Inc., 1928, vol. 2, sect. 35, p. 1909.

8 Ewing, James. *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

tissue that does not occur in the gonad of either male or female. My associates and I found such tissue, we have been able to demonstrate in the walls of a cyst in the tumor columnar, mucus-producing epithelium with typical goblet cells (fig 9). The tissue was entirely quiescent and was taking no part in the active proliferation shown by the actual tumor cells. This structure, since it is foreign to ovary or testis, puts the tumor into the group of teratomas.

With regard to the question of recurrence, the number of mitotic figures and the cellularity of the tumor would ordinarily stamp it as malignant. However, it was well encapsulated everywhere except at the point of omental attachment. There is good physiologic evidence that the cells showed activity comparable to that of normal endocrine tissue. The Leydig cells have been thought to be holocrine, liberating their hormone only on disintegration, and it might be supposed that the cellular division, observed chiefly in the more immature fusiform elements, was only such as was necessary to provide for the replacement of the functioning cells. In this case the tumor may prove, in fact, to be benign.

Nothing was noted to indicate the cell type from which the tumor arose. Meyer<sup>2</sup> considered the ovarian medullary cords of Kolliker the probable origin of such a growth, but Fell<sup>9</sup> traced directly to the germinal peritoneum masculine tissue which had changed the sexual characteristics of a number of hens. It is significant, too, that other tissues of neighboring embryonic origin have the power of elaborating the male hormone under special circumstances, as is seen in the virilism accompanying tumors of the adrenal glands. In addition, it has been suggested that displaced bits of fetal tissue might be the source of the tumor. Such fetal rests often accompany various anomalies, and my patient gave evidence of developmental defects in the reproductive system, noted in the accessory ovarian tissue present in the mass attached to the left oviduct. Since the small nodule in the tubal wall was microscopically typical of rete testis (fig 11), it seems probable that undifferentiated tissue was present in this location and that the tissue, under the stimulus of the male hormone from the tumor, developed in a masculine direction. It is not unlikely, therefore, that a similar group of fetal cells in the ovary, growing in response to an unknown stimulus, might well have been the source of the patient's tumor.

Precedent for the development of masculine tissue in females has been noted in sex reversal in lower animals, in a moth by Goldschmidt,<sup>10</sup>

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<sup>9</sup> Fell, H. B. Histological Studies on the Gonads of the Fowl. I. The Histological Basis of Sex Reversal, *Brit J Exper Biol* **1** 97, 1923.

<sup>10</sup> Goldschmidt, R. Mechanismus und Physiologie der Geschlechtsbestimmung, Berlin, Gebruder Borntraeger, 1920, quoted by Crew<sup>14b</sup>.

in fish by Essenberg,<sup>11</sup> in frogs by Witschi<sup>12</sup> and by Crew,<sup>13</sup> and in fowls by Crew<sup>14</sup> and by a group of other workers whose reports were summarized by Fell.<sup>9</sup> Crew<sup>14</sup> reported that the formation of a malignant tumor with a similar change in the sexual characteristics has occurred in hens, but I have been unable to find the original descriptions of the tumors. Greenwood and Blyth<sup>15</sup> reported active feminization of a capon due to a malignant tumor similar to the embryonic carcinoma of the human testis. All the reports, except those of the malignant tumors, told of more or less complete formation of a testis, which in some instances was functional.

The possible rôle of genetics in such phenomena is worthy of consideration. It is significant that in the cases of functional sexual reversal just described the ratio between the sexes in the offspring was such as to indicate that abnormal genetics played no part.

In conclusion, if one accepts as the diagnostic criterion for a teratoma that it contains tissue not found in the organ of origin or its homologs, it is proper to conclude that the ovarian tumor removed from my patient was of that group. Clinically the growth was identical, however, with the arrhenoblastomas, and pathologically it was highly suggestive at least of the more undifferentiated types of this tumor as they have been described. This suggests that the previously reported arrhenoblastomas may have been a special type of teratoma.

#### SUMMARY

A case of an ovarian tumor that falls into the group of twenty-nine previously reported cases of arrhenomastoma is reported.

The tumor consisted chiefly of testicular interstitial cells and embryonic mesodermal fibrous tissue but also contained tissue which is not found in the gonad of either sex.

The tumor is believed to be a special form of teratoma.

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11 Essenberg, J. M. Sex Differentiation in the Viviparous Teleost, *Xiphorus Helleri*. *Biol. Bull.* **45**: 49, 1923, quoted by Crew.<sup>14b</sup>

12 Witschi, E. *Am. Naturalist* **55**: 529, 1921, quoted by Crew.<sup>14b</sup>

13 Crew, F. A. E. A Description of Certain Abnormalities of the Reproductive System Found in Frogs and a Suggestion as to Their Possible Significance, *Proc. Roy. Soc. Edinburgh* **20**: 236, 1921.

14 Crew, F. A. E. (a) Studies in Intersexuality. II [Fowl], *Proc. Roy. Soc., London, s. B.* **95**: 256, 1923, (b) The Genetics of Sexuality in Animals, New York, The Macmillan Company, 1927.

15 Greenwood, A. W., and Blyth, J. S. S. Reversal of the Secondary Sexual Characters in the Fowl. A Castrated Brown Leghorn Male Which Assumed Female Characters, *J. Genetics* **26**: 199 (Oct.) 1932.

# PROLIFERATIVE ENDOPHLEBITIS (PHLEBOSCLEROSIS)

REPORT OF A CASE

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AND

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Proliferation of the intima of the peripheral veins is a condition to which little attention has been directed in clinical medicine. The reason for this is readily understood when one reads in an eminent and authoritative system of internal medicine<sup>1</sup> that the disease (phlebosclerosis) produces no clinical symptoms. The few notes that appear in the literature deal mainly with a pathologic description of the lesions.

The term "phlebosclerosis," commonly used for this condition, suggests that the pathologic alteration in the veins is comparable to that seen in the arteries in arteriosclerosis. For this reason we prefer to call it "proliferative endophlebitis," although the condition does not appear to be inflammatory. "Proliferative endophlebotis" would perhaps be more accurate, since the term is noncommittal as to etiology, but it does not sound well.

The purpose of this communication is to report a case in which there was presented a clinical syndrome of chronic partial venous obstruction with the pathologic finding of proliferative endophlebitis.

## REPORT OF CASE

*History*—Mrs B K J, aged 24, was admitted to the University of Chicago Clinics on July 10, 1934, referred by Dr W J Corcoran. She complained that she had pains in the muscles of the legs on standing and that the condition was of more than two years' duration. She stated that she had become pregnant for the first time in July 1931. Four months later she noticed a mottled discoloration of the feet, gradually extending to the knees. This condition appeared only when the legs were dependent, particularly when she stood. It was not associated with edema or evidence of thrombophlebitis. There was no toxemia of pregnancy. Labor, which occurred at term, and the postpartum period were normal.

One month after delivery the superficial veins of the legs seemed to swell, and she began to have dull aching pain in both calves. The pains gradually

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Presented before the Chicago Pathological Society on Feb 11, 1935

From the Division of Neurology and Neurosurgery of the University of Chicago Clinics

1 Mohr, L., and Staehelin, R. Handbuch der inneren Medizin, Berlin, Julius Springer, 1928



increased and extended up the medial sides of the thigh to the groins. The discomfort appeared when she was standing, and it was relieved when she walked or lay down. The muscles of the calves seemed firm on palpation. At about this time the veins of the arms were affected similarly but to a lesser degree than those in the legs, with tenderness along the lateral sides of the arms, mottling of the skin and cyanosis of the fingers when dependent. The condition in the arms lasted only a short time, but that in the lower extremities was persistent. Examinations always failed to reveal varicose veins. Of the forms of treatment that were given,



*A*, photomicrograph of a transverse section of a vein showing marked thickening of the subendothelial layer and absence of inflammatory reaction (hematoxylin and eosin,  $\times 34$ ), *B*, photomicrograph of the same section showing abundant reticulin network (Laidlaw's silver impregnation,  $\times 34$ )

contrast baths seemed to lessen the stiffness of the musculature of the calves, and elastic stockings gave considerable symptomatic relief.

At no time did intermittent claudication occur or attacks suggesting vascular spasm. Exposure to cold did not increase the symptoms, emotional stress occasionally seemed to aggravate the discomfort. There was never any edema of the extremities.

Moderate leukorrhea had been present since the pregnancy, but it decreased slightly after cauterization of the cervix. The past and family histories were not significant.

*Examination*—The patient was well nourished and in excellent general health. The principal finding was tenderness of the superficial veins of the lower extremities, including the saphenous veins. Some of the smaller ones, especially those over the lower part of the tibia, were distinctly thickened, forming visible ridges beneath the skin. When the patient stood the feet and legs became cool, purplish and mottled. She then complained that there was aching of the feet and calves, this was relieved by massage or walking as well as by lying down. No blanching appeared when the legs were elevated. Trendelenburg's test was negative. The peripheral arteries were all soft and pulsated well. The pulse rate was 80 per minute. The blood pressure was 110 systolic and 68 diastolic in the brachial arteries and 140 systolic and 85 diastolic in the femoral arteries. Several small firm lymph nodes, not tender, were palpable in the inguinal regions and single ones in the axillae. Neurologic examination disclosed lively tendon reflexes and a bilateral Hoffmann sign but no Babinski sign, the palms were moist. The heart and other viscera were normal. Aside from slight leukorrhea, examination of the pelvis disclosed no abnormal condition.

Routine laboratory tests, including the Wassermann, were all negative.

The taking of temperatures of the skin over various parts of the body showed that the feet were 5 C (9 F) cooler than the rest of the body. Warming the upper extremities and the trunk did not influence the temperature of the feet. Under local anesthesia a small segment of a thickened vein over the lower part of the right tibia was removed for histologic examination. Following this procedure both feet curiously became warmer, their temperature equaling that of the rest of the body. The patient stated that this was the first time in two years that the feet had been definitely warm.

After discharge from the hospital, the patient wrote that the feet remained warm for one week. Then, one night, they became chilled, and the previous cool and mottled state returned.

*Description of Vein*—The removed segment of a vein was narrow and white, and its walls were stiff. The lumen remained open. Microscopic preparations stained by various specific methods showed the great thickening of the wall (fig, A). This was due largely to an increase in the collagen affecting particularly the intima directly beneath the endothelium. In this region there was an abundant network of fine reticulin fibrils (fig, B). The intima varied considerably in thickness. The endothelium was for the most part normal, but in places the cells appeared swollen and more numerous. The other layers were less affected, the media showing perhaps moderate fibrosis and the adventitia little change. Sections stained for elastic tissue showed splitting of the intimal elastic fibers. There was no cellular infiltration, nor any evidence of previous thrombosis. Calcific or fatty change had not taken place.

*Comment*—The symptoms which this patient presented indicate interference with the return of blood from the lower extremities. Discomfort was present when the parts were dependent and inactive, elevation of the extremities or muscular exercise alleviated the symptoms. The veins were palpably thickened and tender, on histologic examination they showed fibrotic proliferative changes especially in the intima. The pathologic features disclosed are similar to those reported by

Stahl and Zeh<sup>2</sup> with the exception that their patient showed calcification of the intima. These authors presented a thorough review of the literature. More recently in this country Hauswirth and Eisenberg<sup>3</sup> discussed the condition, regarding it as much more common than hitherto considered. In their experience the lesions do not cause clinical disturbance of circulatory function.

#### SUMMARY

A case of proliferative endophlebitis is presented which appears to be unique in that the lesions were associated with symptoms definitely indicative of impairment of the venous return.

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2 Stahl, R., and Zeh, F. Ueber Sklerose der peripheren Venen, *Virchows Arch f path Anat* **242** 70, 1923.

3 Hauswirth, L., and Eisenberg, A. A. Disseminated Venofibrosis (Phleboscclerosis), *Arch Path* **11** 857 (June) 1931.

# Progress in Internal Medicine

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## DISEASES OF THE HEART

A REVIEW OF SOME CONTRIBUTIONS MADE DURING 1935

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AND

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The number of papers relating to heart disease published during 1935 was amazingly large. Obviously only a few can be reviewed. As it is, we have been insensibly led to greater length than was first planned. The material has been organized very simply with the view of better correlating the various aspects of a particular problem or disease.

### PHYSIOLOGY AND EXPERIMENTAL PATHOLOGY

Some of the reports which might properly be placed under this heading are discussed appropriately in other sections.

Rytand and Dock<sup>1</sup> have made an interesting study of cardiac hypertrophy. Renal insufficiency was produced in one group of rats, and the hypertrophied hearts were compared with the hearts of rats fed desiccated thyroid and with the hearts of normal controls.

The authors found that the heart of the rat made hypertensive by deprivation of renal tissue reacts by an increase in the weight of its left ventricle alone, while the cavity of the left ventricle not only does not dilate but is relatively small in comparison with the weight of its surrounding myocardium. In the concentric hypertrophy so induced, the myocardial fibers of the left ventricle are increased in width and decreased in length. The heart of the rat fed thyroid extract becomes heavier in both ventricles equally, while the dilatation of the left ventricle closely parallels hypertrophy. In the eccentric hypertrophy so induced the myocardial fibers do not show a significant change in width, but they lengthen greatly. From a consideration of cardiodynamics it is shown that concentric hypertrophy is the optimum compensatory mechanism for the hypertensive heart, which must expel a normal minute output against an increased peripheral resistance in the systemic

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From the Cardiac Clinic of the Massachusetts General Hospital

1 Rytand, David A., and Dock, W. Experimental Concentric and Eccentric Cardiac Hypertrophy in Rats, *Arch Int Med* **56** 511 (Sept) 1935

circuit, while eccentric hypertrophy is the optimum compensatory mechanism for the heart which must expel an increased minute output against presumably normal peripheral resistance

Evans, Grande and Hsu<sup>2</sup> have shown that the working heart, in contrast to skeletal muscle, shows the ability to utilize lactic acid derived from the blood and that the rate of such utilization is roughly proportional to the amount of work done and the concentration of lactic acid in the perfusing blood. It was shown furthermore<sup>3</sup> that if the heart is made to utilize more lactic acid by the addition of sodium lactate to the perfusing blood, increase of the coronary flow, decrease of heart rate and lowering of venous pressure can be observed. Control experiments were performed with sugar and sodium bicarbonate in similar concentration, but the beneficial effect was not usually observed. Bogue, Evans and Hsu expressed the opinion that it is therefore highly probable that the effect is specific to the lactate ion. They stated that in the resting state of the intact body the lactate content of the blood is at its basic level and consequently its usage by the heart is small. During strenuous muscular exertion, however, the lactate content of the blood is enormously increased, and at the same time the heart is required to do more work. It is under these conditions that the ability of the heart to utilize lactic acid shows its full significance. Not only does lactic acid promote contractility of the cardiac muscle, but, like carbon dioxide, it tends to slow the rate and increase the efficiency. Since the rate at which the lactic acid penetrates into the cardiac tissues is greater than that at which sugar is absorbed, lactic acid is more readily available to meet the increased demands for fuel by the heart. Moreover, the rate of utilization is facilitated by the property of lactic acid itself to increase the coronary flow.

Harris, Jones and Aldred<sup>4</sup> have found that under resting conditions the lactic acid content of the blood is increased in cases of cardiac failure and that this increase stands in a definite relation to the degree of failure. The increase in lactic acid content after a standard exercise is greater the greater the degree of cardiac failure. They express the opinion that the accumulation of lactic acid in the blood in cases of heart disease is probably due to defective oxygenation but may be due to accumulation of carbon dioxide in the tissue of the respiratory center, which brings about alkalosis and an associated rise in the lactic acid

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2 Evans, C L, Grande, F, and Hsu, F Y. Glucose and Lactate Consumption of Dog's Heart, *Quart J Exper Physiol* **24** 347, 1935

3 Bogue, J Y, Evans, C L, and Hsu, F Y. The Significance of Lactic Acid Uptake by the Mammalian Heart, *J Physiol* **84** 55P, 1935

4 Harris, I, Jones, E W, and Aldred, C N. Blood  $p_H$  and Lactic Acid in Different Types of Heart Disease, *Quart J Med* **4** 407, 1935

content of the blood Except in extremely severe conditions the  $p_H$  of the blood is normal in the different types of heart disease

Weiss and Ellis<sup>5</sup> compared the utilization of oxygen and the production of lactic acid in the upper and lower extremities in normal subjects and in patients having heart disease with and without congestive failure During rest, the average oxygen utilization was essentially the same in the arm and in the leg, and the values were similar for normal persons and for patients with heart disease without congestion When congestive failure was present there was an increased peripheral utilization of oxygen, which is evidence that the blood flow through the extremities was reduced On standing, the oxygen utilization of the extremities increased in all groups, as a result, in part at least, of a decrease in blood flow, immediately after exercise the oxygen utilization increased markedly The average level of the lactic acid in the extremities during rest was between 12 and 14 mg per hundred cubic centimeters for all groups, this does not agree with the results of others, who found an increased concentration of the lactic acid of the blood in patients with severe circulatory failure Immediately after exercise the lactic acid content of the blood of the femoral vein draining the active muscle more than doubled, it then fell rapidly during the next ten minutes and more slowly in the succeeding ten minutes, but it did not reach the level observed during rest within twenty minutes The lactic acid content of the venous blood of the inactive arm rose slightly immediately after the exercise, but in ten minutes it was similar to that of the leg, as a result of the mixing effect of the circulation With the increasing severity of circulatory failure, there was a tendency for the lactic acid content of the blood of the femoral vein to rise to a higher level than normal immediately after exercise and to fall more slowly

Weiss and Ellis commented on their observations as follows

As a result of these studies we consider that there is no evidence of a primary disturbance of the peripheral circulation as the precipitating factor in heart failure There is evidence, however, that the peripheral circulation does not play a purely passive rôle, as was once widely believed In normal persons, the cardiovascular functions can be increased efficiently and a certain amount of the load removed from the heart itself by peripheral vascular reflexes which tend to shunt blood where it is most needed and under greater pressure, particularly by increased oxygen utilization The same factors, to a greater degree, tend to operate in patients with heart disease, with and without evidence of failure With the aid of the peripheral circulation, compensation for an inadequate cardiac function may be achieved

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5 Weiss, Soma, and Ellis, Laurence, B Oxygen Utilization and Lactic Acid Production in the Extremities During Rest and Exercise in Subjects with Normal and in Those with Diseased Cardiovascular Systems, *Arch Int Med* 55 665 (April) 1935

## ELECTROCARDIOGRAPHY

Dale<sup>6</sup> briefly referred to the many attempts made in the past to correlate the different phases of the electrocardiogram with other events in the cardiac cycle, such as the contraction process or the production of lactic acid. Since the discovery that the production of lactic acid in both cardiac and skeletal muscle is abolished by poisoning with iodoacetic acid, it has been possible to determine whether there is a correlation between any phase of the electrocardiogram and the formation of lactic acid. The frog's ventricle perfused with thoroughly aerated Ringer's solution has been shown to derive its energy from at least two sources, of which one is carbohydrate and the other, for want of more precise knowledge of its nature, may be termed noncarbohydrate. If oxygen is withheld from the perfusing solution, the frog's ventricle derives its energy solely from carbohydrate and contracts normally provided the perfusion medium is alkaline, thus allowing the muscle to excrete the lactic acid formed. On the other hand, a ventricle in which carbohydrate metabolism has been excluded by poisoning with iodoacetic acid can contract normally provided the perfusion solution is thoroughly oxygenated. It is possible, therefore, by subjecting a ventricle to the appropriate conditions to cause it to derive its energy from normal mixed carbohydrate and noncarbohydrate, pure carbohydrate and pure noncarbohydrate. Experiments were carried out to determine whether the type of metabolism has any influence on the electrical response. The change from mixed metabolism to pure carbohydrate metabolism produced a definite though slight effect on the mechanical and electrical responses, diminishing the former and increasing the duration of the latter, while the change to pure noncarbohydrate metabolism produced no definite effect. Dale concluded that it is possible to abolish the production of lactic acid in the frog's ventricle without affecting the duration or form of the electrical response.

Kountz and his co-workers<sup>7</sup> have made important and interesting electrocardiographic studies on revived perfused human hearts. Immediately after death the chest was opened, the pericardium incised and the heart perfused. In most cases the cardiac nerves were cut. Of a

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6 Dale, A. S. The Relation Between Metabolic Processes and the Ventricular Electrogram, *J. Physiol.* **84** 433, 1935.

7 Kountz, W. B., Prinzmetal, M., Pearson, E. F., and Koenig, K. F. The Effect of Position of the Heart on the Electrocardiogram. I. The Electrocardiogram in Revived Perfused Human Hearts in Normal Position, *Am. Heart J.* **10** 605, 1935. Kountz, W. B., Prinzmetal, M., and Smith, J. R. The Effect of Position of the Heart on the Electrocardiogram. II. Observations upon the Electrocardiogram Obtained from a Dog's Heart Placed in the Human Pericardial Cavity, *ibid.* **10** 614, 1935. III. Observations upon the Electrocardiogram in the Monkey, *ibid.* **10** 623, 1935.

total of 37 cases studied by this method, normal-appearing electrocardiograms were obtained in 8, and these were further investigated. Four general types of extrasystoles were observed. Discordant curves in which the initial ventricular deflection was up in lead I and down in lead III were obtained by stimulating the right ventricle everywhere except at the conus, where stimulation produced concordant extrasystoles in which the initial ventricular deflection was upright in all three leads. Discordant curves in which the initial deflection was down in lead I and up in lead III were obtained from the left ventricle except at the apex, where stimulation produced concordant extrasystoles in which the initial ventricular deflection was down in all three leads. When the right bundle branch was cut with the heart in the normal position, the initial ventricular deflection of the electrocardiogram was usually down in lead I and up in lead III, when the left bundle branch was cut, the initial ventricular deflection of the electrocardiogram was up in lead I and down in lead III. Shift of the heart to the right caused left axis deviation (present terminology) in the electrocardiogram, and shift to the left, right axis deviation. Rotation of the heart clockwise caused right axis deviation, while rotation counter clockwise caused left axis deviation.

Observations on the electrocardiograms obtained from a dog's heart placed in the human pericardial cavity and from the hearts of monkeys were in agreement with the observations just described.

The results reported by Kountz and his co-workers confirm the correctness of the newer terminology for bundle branch block and the recent opinion that what have been considered right ventricular extrasystoles are in reality left ventricular extrasystoles, and vice versa. Furthermore, the effect of shifting the heart confirms the view that what has been considered right axis deviation is in reality left axis deviation, and vice versa.

Maham,<sup>8</sup> however, on the basis of careful histologic studies on the bundle of His and its branches, expressed the belief that the old classic terminology in regard to bundle branch block is correct.

There have been many reports<sup>9</sup> concerning the electrocardiogram in cases of myocardial infarction, only a few are mentioned. They

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8 Maham, Ivan. Nouvelles recherches sur les lésions du faisceau de His-Tawara. Le bloc de branche gauche et sa pathogenie. La septite mitrale, *Ann de med* **38** 185, 1935.

9 Sprague, H. B., and Orgain, E. S. Electrocardiographic Study of Cases of Coronary Occlusion Proved at Autopsy at the Massachusetts General Hospital, 1914-1934, *New England J Med* **212** 903, 1935. Barnes, Arlie R. Electrocardiogram in Myocardial Infarction. Review of One Hundred and Seven Clinical Cases and One Hundred and Eight Cases Proved at Necropsy, *Arch Int Med* **55** 457 (March) 1935. Jervell, A. Elektrokardiographische Befunde bei Herzinfarkt,



contain the latest knowledge concerning this important branch of electrocardiography

The precordial electrocardiographic "lead" appears to have a definite value, although to what degree it may complement the usual three leads is not yet fully established

It seems wise to advise for routine examinations the use of a single chest lead, with the precordium at the cardiac apex the site of application for one electrode and the left leg for the other. It is well to label this lead as lead IV, disregarding for the present at least the complication of other chest leads, leads V to IX, inclusive. It has not been shown that chest leads other than lead IV are of significant practical value.

We agree with Roth<sup>10</sup> that many reports concerning lead IV "appear to be colored by an unwarranted enthusiasm on the subject, leading on the one hand to an overemphasis of the value of chest leads, and on the other to a tendency to underrate the significance of abnormalities in the standard leads." A considerably longer time and much more work are needed before the full and correct evaluation of lead IV can be made.

During 1935 several publications have appeared, some<sup>11</sup> of which may be referred to for a summary of the knowledge on lead IV to date, especially in regard to its value in the diagnosis of heart disease with involvement of the coronary arteries.

The use of chest leads as well as limb leads has enabled Wolferth and Wood<sup>12</sup> to predict correctly the site of the infarct in each of their twenty cases of acute coronary occlusion in which autopsy was performed during the past three years. They pointed to several factors which may confuse the observer in attempting to locate the lesion and

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Acta med Scandinav, supp 68, 1935, p 1. Johnston, F D, Hill, I G W, and Wilson, Frank N. The Form of the Electrocardiogram in Experimental Myocardial Infarction II, Am Heart J 10 889, 1935. Wilson, Frank N, Hill, I G W, and Johnston, F D. The Form of the Electrocardiogram in Experimental Myocardial Infarction III, *ibid* 10 903, 1935. Wilson, Frank N, Johnston, F D, and Hill, I G W. The Form of the Electrocardiogram in Experimental Myocardial Infarction IV, *ibid* 10 1025, 1935.

10 Roth, I R. On the Use of Chest Leads in Clinical Electrocardiography, Am Heart J 10 798, 1935.

11 Faulkner, James M. The Electrocardiographic Diagnosis of Acute Cardiac Infarction with Special Reference to the Value of Precordial Leads, New England J Med 213 1215, 1935. Bohning, A, and Katz, L N. The Four Lead Electrocardiogram in Coronary Sclerosis. A Study of a Series of Consecutive Patients, Am J M Sc 189 833, 1935. Roth<sup>10</sup>

12 Wolferth, C C, and Wood, F C. Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of the Left Ventricle, Arch Int Med 55 77 (July) 1935.

reported a group of ten cases in which there were electrocardiographic indications of acute lesions in both the anterior and the posterior wall of the left ventricle. In some cases the tracings suggested that the main lesion was anterior, and in others, that the main infarct was posterior. The most helpful signs were certain changes in the RS-T interval and in the QRS complex. In two of the ten cases necropsy was performed, revealing in each instance lesions involving part of both the anterior and the posterior wall of the left ventricle.

In following the effect of the rheumatic process on the heart with the aid of serial electrocardiography, Levy and Bruenn<sup>13</sup> found that the additional use of lead IV in certain instances revealed evidence of active carditis when in the usual three leads either no changes in form were apparent or the alterations noted were regarded as equivocal. About the only abnormalities noted in lead IV were variations in the form and amplitude of the T wave. Because of the variability of the T wave in lead IV, Levy and Bruenn pointed out that only changes in its form occurring in records taken on the same patient at different times may be regarded as evidence indicating alterations in the state of the myocardium. They stated, however, that such successive changes, while showing that the heart is affected and that the lesions are not in a quiescent state, are not specific indications of rheumatic fever.

Strauss and Katz<sup>14</sup> have studied the effect of digitalis on the appearance of lead IV. Seven normal persons were digitalized to the point of toxicity, and the appearance of the four lead electrocardiograms after medication was compared with that of the tracings made before digitalization was begun. The authors also studied six patients with various types of cardiac lesions in whom digitalization was demonstrable clinically and in the three usual electrocardiographic leads. The chief changes observed in lead IV were in the ST segment and the T wave, and these were reversible when the administration of digitalis was discontinued. In several instances the contour of lead IV closely resembled that seen after recent coronary occlusion, and Strauss and Katz emphasized the need of caution in interpreting these records.

Among a number of electrocardiographic clinical studies,<sup>15</sup> that of Schwab and Herrmann on alterations of the electrocardiogram in dis-

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13 Levy, R. L., and Bruenn, H. G. Precordial Lead of Electrocardiogram (Lead IV) as an Aid in Recognition of Active Carditis in Rheumatic Fever, *Am Heart J* **10** 881, 1935.

14 Strauss, H., and Katz, L. N. Effect of Digitalis on the Appearance of Lead IV, *Am Heart J* **10** 546, 1935.

15 Schwab, Edward H., and Herrmann, George. Alterations of the Electrocardiogram in Diseases of the Pericardium, *Arch Int Med* **55** 917 (June) 1935.  
Rykert, H. E., and Hepburn, J. Electrocardiographic Abnormalities Character-

ease of the pericardium is of considerable interest. They completely reviewed the medical literature on this subject and reported in detail 7 cases of pericardial disease of various types, including serial electrocardiographic studies. The chief electrocardiographic alterations were found to be a decrease in the voltage of the QRS complex, deviation of the RS-T segment from the iso-electric level and variations in the form and amplitude of the T wave. An evaluation of the electrocardiographic differences between pericardial disease and cardiac infarction is presented, and the absence of significant abnormalities of the Q wave in cases of pericardial pathologic processes is stressed. No information of differential value was derived from the use of lead IV.

New and simple methods<sup>16</sup> of avoiding high resistance and overshooting in taking standardized electrocardiograms have been described. The procedure involves the use of pastes which easily reduce cutaneous resistance below 2,000 ohms and form a nonpolarizing contact between the skin and the electrode.

#### ROENTGENOLOGY

Few articles concerning roentgen examination of the heart and aorta have been published during 1935. There is continued interest in kymography,<sup>17</sup> especially in Europe, but there have been no recent important contributions.

Warfield<sup>18</sup> wrote an interesting paper on the roentgen diagnosis of aneurysms of the innominate artery, stressing particularly methods of differential diagnosis from other tumors in the mediastinum and the necessity of first demonstrating the presence of aortitis.

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istic of Certain Cases of Hypertension, *Am Heart J* **10** 942, 1935. Graybiel, Ashton, and White, Paul D. Inversion of the T-Wave in Leads I or II of the Electrocardiogram in Young Individuals with Neurocirculatory Asthenia, with Thyrotoxicosis, in Relation to Certain Infections, and Following Paroxysmal Ventricular Tachycardia, *ibid* **10** 345, 1935. Aschenbrenner, R., and Bamberger, P. Elektrokardiographische Untersuchungen an spasmophilen Kindern, *Klin Wchnschr* **14** 1494, 1935.

16 Jenks, James L., Jr., and Graybiel, Ashton. A New and Simple Method of Avoiding High Resistance and Over-Shooting in Taking Standardized Electrocardiograms, *Am Heart J* **10** 693, 1935. Russell, H. B. The Use of Cambridge Electrode Jelly, *Lancet* **2** 1173, 1935.

17 Kahlstorf, A., and Ohnesorge, E. Die diagnostische Bedeutung der pulsatorischen Aortenbewegungen im Flächenkymogramm, *Fortschr a d Geb d Röntgentrahl* **51** 22, 1935. Holst, L., Klioner, I., Koppelman, S., and Speranski, N. Die Flächenkymographie des Herzens, *ibid* **51** 454, 1935. Klioner, I., and Ivanov, N. Die normale Herzkurve und die physiologischen Veränderungen derselben im Flächenkymogramm, *ibid* **51** 469, 1935.

18 Warfield, C. H. Roentgen Diagnosis of Aneurysms of the Innominate Artery, *Am J Roentgenol* **33** 350, 1935.

Brown and McCarthy<sup>19</sup> studied the abnormal conditions which affect the position of the esophagus. While the material presented is not new, it is well discussed.

Parade<sup>20</sup> called attention to 2 cases of mitral stenosis in which roentgen therapy was followed by auricular fibrillation. In 1 instance the heart was directly exposed to the rays, in the other it was not. Parade suggested that substances liberated in the course of the roentgenotherapy exert a harmful effect on the heart or its regulatory mechanism. The experiments of Nahum and Hoff<sup>21</sup> may be remembered with interest in this connection.

Udvardy<sup>22</sup> found no uniform configuration of the heart in cases of emphysema, for in the various stages of this disorder the heart undergoes various changes. At first the size of the heart is reduced because the thorax is fixed in inspiration and the intrapulmonary pressure is raised, the entire picture, the lungs as well as the heart, are seen as in Valsalva's experiment. With the progress of the disease, the right ventricle gradually becomes larger, and finally the entire heart enlarges to such a size that a "mitral configuration" is suggested, especially as the pulmonary arc is prominent.

#### HEART SOUNDS AND MURMURS

A large number of papers<sup>23</sup> have appeared on heart murmurs and sounds, including gallop rhythm. Nothing new of great clinical sig-

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19 Brown, S., and McCarthy, J. E. Study of the Esophagus in Relation to the Heart, Aorta and Thoracic Cage, *Radiology* **24** 131, 1935.

20 Parade, G. W. Herzscheidungung bei Rontgenbestrahlung, *Med. Klin.* **31** 1396, 1935.

21 Nahum, L. H., and Hoff, H. E. Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl-B-Methylcholine Chloride, with Observations on the Role of the Vagus and Some Exciting Agents in the Genesis of Auricular Fibrillation, *J. A. M. A.* **105** 254 (July 27) 1935.

22 Udvardy, L. Form- und Grossenveränderungen des Herzens bei Erkrankungen der Lungen, Pulmonalsklerose, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **52** 115, 1935.

23 Duchosal, P. Nouvelles recherches graphiques sur le bruit de galop, *Arch. mal. du cœur* **28** 345, 1935. Wolferth, Charles C., and Margolies, Alexander. Asynchronism in Contraction of the Ventricles in the So-Called Common Type of Bundle-Branch Block. Its Bearing on the Determination of the Site of the Significant Lesion and on the Mechanism of Split First and Second Heart Sound, *Am. Heart J.* **10** 425, 1935. The Influence of Varying As-Vs Intervals on Split First Heart Sounds. Its Bearing on the Cause of Split Sounds and the Mechanism of the First Sound, *J. Clin. Investigation* **14** 605, 1935. Thompson, W. P., and Levine, S. A. Systolic Gallop Rhythm. Clinical Study, *New England J. Med.* **213** 1021, 1935. Friedlander, R. D., and Brown, M. G. The Systolic Murmur. Further Observations on Its Clinical Significance, *Ann. Int. Med.* **8** 893, 1935. Bramwell, Crighton. Sounds and Murmurs Produced by Auricular Systole, *Quart.*

nificance is reported, and owing to considerations of space the papers are not reviewed

#### CONGENITAL HEART DISEASE

No contribution of great importance has been presented under this heading, although many interesting cases have been reported

#### RHEUMATIC HEART DISEASE

Inquiry into the cause of rheumatic fever has been given direction, largely, by the fact that tonsillitis or pharyngitis frequently precedes the rheumatic process. Naturally, organisms responsible for infections of the upper portion of the respiratory tract have been studied exhaustively. The rarity of the finding of bacteria in rheumatic inflammatory lesions, however, led to the suggestion that these lesions may be allergic. This supposition has gained support chiefly on histopathologic grounds and on the basis of the clinical fact that a "silent" or "latent" period intervenes, usually, between the rheumatic attack and the preceding infection of the respiratory tract.

During the past few years interest has centered chiefly on the hemolytic streptococci, and great efforts have been made to establish a constant relationship between a focus of streptococcic infection and rheumatic fever. Cultural methods have been supplanted largely by the more delicate and indirect immunologic reactions. These include the precipitation, agglutination and complement-fixation reactions and the determination of antihemolysins, antistreptolysins and antifibrinolysins. In the past year a number of reports<sup>24</sup> have appeared concerning one or another of the aforementioned procedures. Although the results of different workers are not in agreement, evidence shows that there is often a relationship between the development and intensity of the immune

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J Med **4** 139, 1935, Gallop Rhythm, *ibid* **4** 149, 1935 de Chatel, A. Veränderungen des ersten Herztones bei Ueberleitungsstörungen, *Klin Wchnschr* **14** 1004, 1935 Bierring, Walter L., Bone, H. C., and Lockhart, M. L. Use of the Electrosthethograph for Recording Heart Sounds, *J A M A* **104** 628 (Feb 23) 1935 Routier, Daniel, and Van Heerswynghe, J. A propos du bruit de galop Etude phonocardiographique, *Arch d mal du cœur* **28** 629, 1935

<sup>24</sup> Beck, A., and Coste, F. Streptococcus Complement-Fixation Reaction in Rheumatic Diseases, *Brit J Exper Path* **16** 20, 1935 Coburn, Alvin F., and Pauli, Ruth H. Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process I, II and III, *J Exper Med* **62** 129, 137 and 159, 1935, IV, V and VI, *J Clin Investigation* **14** 755, 763 and 769, 1935 Schlesinger, B., Signy, A. G., and Payne, W. W. Further Studies on the Aetiology of Acute Rheumatism, *Lancet* **1** 1090, 1935 Wilson, Max G., Wheeler, George W., and Leask, Marguerite M. The Relation of Upper Respiratory Infections to Rheumatic Fever in Children II. Antihemolysin Titres in Respiratory Infections and Their Significance in Rheumatic Fever in Children, *J Clin Investigation* **14** 333, 1935

response to hemolytic streptococci and those of acute rheumatism. However, there are frequent exceptions to this close relationship, and some of these will now be considered.

Occasional instances of reactivation of rheumatic fever by events other than streptococcic infection have attracted the attention of Bland and Jones.<sup>25</sup> Transient and unexplained elevations of temperature, accidents, operations and various infections were found to have a relationship to relapses in cases of rheumatic fever similar to that of streptococcic infection. Especially interesting was the case of a girl with severe chorea and minimal rheumatic heart disease, in whom a rectal temperature of 108.9 F developed after the third daily injection of stock typhoid-paratyphoid vaccine. The chorea became less severe, but reactivation of the rheumatic fever occurred two weeks later. Stimulated by this observation, Bland and Jones selected 10 young persons for further study. All were in excellent general physical condition but exhibited evidence, chiefly from laboratory examination, of low grade chronic rheumatic fever. These 10 patients received twelve intravenous injections of 0.1 cc of typhoid-paratyphoid vaccine, which caused a slight febrile reaction and chill. In 6 instances clinical and laboratory evidence of reactivation of rheumatic fever appeared either immediately after the injection or two or three weeks later. In 4 instances there was no evidence, and in 2 there was slight evidence, of reactivation. These artificially provoked recurrences were mild and led to no significant injury but "reproduced in a striking fashion the rheumatic manifestations which had been previously observed in the individual patient during a naturally occurring recrudescence." These observations led Bland and Jones to conclude that the rôle of infections or other episodes apparently related to the rheumatic process should be regarded as non-specific.

That rheumatic fever may be due to a factor which becomes operative when some predisposing event places the body in a vulnerable state is a commonly held supposition. Important evidence that this factor may be a virus has been advanced by Schlesinger, Signy, Amies and Barnard.<sup>26</sup> They employed methods similar to those used successfully in the identification of the viruses of vaccinia and psittacosis. Pericardial and pleural fluids from patients dying of active rheumatic infection were submitted to centrifugation at high speed. The deposits, shown

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25 Bland, Edward F., and Jones, T. Duckett. Clinical Observations on the Events Preceding the Appearance of Rheumatic Fever, *J. Clin. Investigation* **14**: 633, 1935.

26 Schlesinger, B., Signy, A. G., Amies, C. R., and Barnard, J. E. Aetiology of Acute Rheumatism. Experimental Evidence of a Virus as the Causal Agent, *Lancet* **1** 1145, 1935.

to be sterile by cultural methods, were examined microscopically by dark-field and tinctorial methods as well as according to Barnard's special technic. Particles of uniform character were seen which resembled the elementary bodies observed in diseases known to be caused by a virus. Pericardial fluid from 7 patients was examined in this fashion, and elementary bodies were seen in 6 instances, fluid in which similar bodies were not found came from a patient with a chronic rheumatic infection. Elementary bodies were found in the deposit obtained from the pleural exudate of 1 patient with rheumatic pneumonia. Control fluids failed to show these virus-like particles.

This matter was carried a step further by showing that these elementary bodies are specifically agglutinated by the serums of patients who are suffering from, and successfully resisting, an acute rheumatic infection. Serum of patients with quiescent rheumatism failed to agglutinate these bodies.

The authors made the following suggestions:

the bodies found in the pericardial exudates represent the actual infective agent of acute rheumatism.

The importance of streptococcal infection as a factor in the etiology of the disease is recognized. It is suggested that the lowered resistance produced by such infections enables the virus to enter the body or, if the virus is already lying latent in the tissues, allows it to assume active characters.

Coles<sup>27</sup> claimed to have seen these virus bodies in the pericardial exudate obtained from patients dying not only of rheumatic fever but of various other causes, including accidents, sepsis and malignant leukemia.

The findings of Schlesinger and his co-workers<sup>28</sup> are suggestive despite their incompleteness and are not open to facile criticism. Much remains to be done and already there are attempts to reproduce rheumatic fever in animals known to be susceptible to certain diseases caused by a virus.

Numerous pathologic studies have emphasized the causal relationship between rheumatic fever and vascular injury. Lesions have been described in all orders of vessels from aorta to capillaries. For the greater part these lesions are not considered specific of rheumatic fever, although Aschoff nodules have been described as occurring in several parts of the vascular tree.

The development of nodular lesions in the ascending portion of the aorta during rheumatic fever is well known since the work of Pappenheimer and Von Glahn, Klotz and others. Gross<sup>28</sup> has described the

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27 Coles, A. C. Virus Bodies in the Pericardial Fluid of Rheumatic Fever, *Lancet* 2 125, 1935.

28 Gross, L. Lesions in Roots of Pulmonary Artery and Aorta in Rheumatic Fever, *Am J Path* 11 631, 1935.

lesions found in the roots of the pulmonary artery and aorta, together with their pericardial mantles, in 150 hearts. Sixty-six hearts were from patients with active rheumatic fever, 34 from patients with inactive disease and 50 from normal control persons. In all the patients with active rheumatic disease there was either microscopic pericarditis or acute exudative pericarditis in relation to the roots of the great vessels, which may have accounted for the high incidence of their capillarization (capillarization occurred in over 70 per cent of the patients with inactive as well as active disease and in only 25 per cent of the controls). In patients with active rheumatic fever the incidence of inflammatory and destructive lesions in the pulmonary roots was nearly as high as that of lesions in the aortic roots, although scarring was more conspicuous in the latter. Some of the lesions were similar to those occurring in nonrheumatic controls owing to changes resulting from age, while others were more characteristic. The lower incidence of the more characteristic lesions in the group of patients with inactive disease indicates that healing may sometimes occur.

Gigante,<sup>29</sup> working in Aschoff's laboratory, carefully studied the abdominal aorta and carotid arteries from 30 rheumatic and nonrheumatic patients. He failed to find either Aschoff nodules or specific types of scarring which might have resulted from previous rheumatic involvement. His findings, consequently, are not in accord with those of Klinge, who has described specific rheumatic lesions in the abdominal aorta which, in his opinion, are associated with the development of atherosclerosis.

Gross, Kugel and Epstein<sup>30</sup> have described, classified and compiled statistics on the vascular lesions in the coronary arteries as they occur in cases of active and inactive rheumatic fever. Their conclusions are in general agreement with previous studies in this field. They emphasized the marked vascular damage found in the cases of active disease, which "may be so extensive that it would be difficult if not hazardous to venture an opinion as to whether the vascular or primary myocardial injury is the more significant with regard to the life of the patient." Vascular lesions in the cases of inactive disease were essentially similar to those found in control hearts, but their development was precocious. In the experience of the present authors, however, important disease of the coronary arteries in youth has been found rarely in association with evident rheumatic heart disease or with a past history of rheumatic infection.

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29 Gigante, D. Ueber die Atherose und Atherosklerose der Bauchorta, der Carotiden und der Sinus carotici, und ihre Beziehungen zum Rheumatismus specificus infectiosus, *Beitr z path Anat u z allg Path* **95** 71, 1935.

30 Gross, Louis, Kugel, M. A., and Epstein, E. Z. Lesions of the Coronary Arteries and Their Branches in Rheumatic Fever, *Am J Path* **11** 253, 1935.



Auricular lesions in cases of rheumatic fever have been widely recognized since the publication of studies by MacCallum, Thayer, Von Glahn and others. Gross<sup>31</sup> has examined the left auricle in 87 rheumatic hearts and classified the material into five clinical groups according to the stage of the disease. Of especial interest was the finding of macroscopic lesions in 80 per cent of the cases and of microscopic lesions in 100 per cent. In about 50 per cent of the cases there was microscopic evidence of some lesion in the pericardium overlying the left auricle.

Bland, White and Jones<sup>32</sup> have presented clinical and postmortem observations on a group of 100 young patients with rheumatic heart disease with especial regard to the development of deformity of the mitral valve, and the interpretation of mitral diastolic murmurs. It was found that a period of at least two years from the onset of rheumatic fever was necessary for the development of extensive valvular deformity either with or without stenosis. Of 47 patients who died two years or more after the onset of rheumatic fever, only 20 had frank mitral stenosis. Sixty-eight of the 100 patients had a rumbling mitral diastolic murmur, accompanied by a thrill in 30 instances, which led to a clinical diagnosis of mitral stenosis. Of these 68, only 21 had anatomic stenosis of the mitral orifice, 19 had gross deformity of the cusps without stenosis and the remaining 28 had either no deformity or, at most, minimal thickening of the free margin of the valve. Of these last 28 patients only 2 had aortic regurgitation to a sufficient degree to require consideration of an Austin Flint murmur. Myocardial weakness and ventricular dilatation occurring during the course of active rheumatic fever appeared to be responsible for the production of the mitral diastolic murmur in these patients.

In a group of patients with acute rheumatic heart disease studied clinically, the mitral systolic and diastolic murmurs were found to disappear in a number of instances after the subsidence of the active infection. This clears up the mystery of such an event, the significance of which has been variously interpreted in the past—for example, by the assumption that valvular disease retrogressed or became clinically unrecognizable.

De Graff and Lingg<sup>33</sup> have studied carefully the course of rheumatic heart disease in 644 fatal cases in a total of 1,633 cases coming

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31 Gross, Louis. Lesions of the Left Auricle in Rheumatic Fever, *Am J Path* **11** 711, 1935.

32 Bland, Edward F., White, Paul D., and Jones, T. Duckett. The Development of Mitral Stenosis in Young People with a Discussion of the Frequent Misinterpretation of a Middiastolic Murmur at the Cardiac Apex, *Am Heart J* **10** 995, 1935.

33 De Graff, Arthur C., and Lingg, Claire. The Course of Rheumatic Heart Disease in Adults. I, II and III, *Am Heart J* **10** 459 and 630, 1935.

under observation Of these 644, 55.8 per cent were in male and 44.2 per cent in female patients De Graff and Lingg found that this disease runs its course chiefly within the first four decades The average age at the initial infection was found to be 17 years, that at the first symptom of cardiac insufficiency, 28 years, that at the first appearance of heart failure,<sup>34</sup> 30 years, and that at death, 33 years Mitral valvular disease was found to be more frequent in women, whereas aortic disease was approximately twice as frequent in men Lesions of the tricuspid or the pulmonary valve were comparatively rare Valvular disease in itself afforded no significant information as to prognosis The prognosis became slightly less favorable if the pulmonary or the tricuspid valve was damaged Auricular fibrillation developed in 42.8 per cent of the 644 cases This arrhythmia was usually a late manifestation in rheumatic heart disease, and the highest incidence was found in cases of mitral stenosis Auricular fibrillation per se did not determine prognosis or life expectancy

It is important to distinguish, however, between children who have a first attack of rheumatic infection involving the heart and adults with chronic rheumatic valvular disease because of the fact that younger patients usually die of the rheumatic infection itself while older patients generally die of the late results in the form of heart failure

#### SYPHILITIC DISEASE OF THE HEART AND AORTA

Maynard and his co-workers<sup>35</sup> have published a preliminary report of their investigation designed as a study of the natural history of syphilitic infection in relation to its effect on the cardiovascular system Every syphilitic patient in the Brooklyn Hospital who consented was subjected to a complete cardiovascular examination Of 346 patients thus examined, 145 (41.9 per cent) presented evidence of cardiovascular syphilis This incidence is extremely high, but the criteria for diagnosis set by Maynard and his co-workers seem adequate For example, all the patients with uncomplicated aortitis were known to have been syphilitic, none had suffered from rheumatic fever or arterial hypertension, none was over 49 years of age or presented any evidence of peripheral sclerosis, and all exhibited dilatation of the aorta

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34 Heart failure was considered to be present when symptoms of cardiac insufficiency were so pronounced that the patients were unable to do any work and had to go to bed and remain there for some time

35 Maynard, E. P., Jr., Curran, J. A., Rosen, I. T., Williamson, C. G., and Lingg, Claire. Cardiovascular Syphilis. Early Diagnosis and Clinical Course of Aortitis in Three Hundred and Forty-Six Cases of Syphilis, *Arch. Int. Med.* 55: 873 (June) 1935

Maynard and his co-workers divided their patients into five groups according to the interval between the appearance of a chancre and the time of the cardiovascular study. The incidence of cardiovascular syphilis among patients examined within the first three years was 14 per cent, among those examined within from four to nine years it was 28.6 per cent, among those examined within from ten to nineteen years, 56.8 per cent, among those examined within from twenty to twenty-nine years, 77.8 per cent, and among those examined within thirty or more years, 88.2 per cent. The incidence of symptoms increased progressively in the five groups, heart failure (congestive failure) was found to occur only in the patients in whom aortic insufficiency, aneurysm or involvement of a coronary artery developed. Maynard and his co-workers reached the important conclusion that "involvement of the aorta begins soon after the chancre has appeared and that, in the past, discovery of the presence of the disease has been delayed by the late development of symptoms referable to the heart and more especially by inadequate methods of examination." For final confirmation of this conclusion more pathologic study is required.

Padget and Moore<sup>36</sup> have analyzed the course of the disease in 161 patients with cardiovascular syphilis in respect to the effect of anti-syphilitic treatment. About one third of the patients died in less than a year of observation, these were considered in a separate group, as unamenable to the beneficial effects of antisyphilitic therapy because of the gravity of their disease. Of the remaining two thirds, about half were considered as having had adequate, and half as having received inadequate, treatment. The "mean potential period" of observation was ten years and eight months. The number of deaths due to cardiovascular syphilis was found to be 1.62 times as great in the poorly treated as in the well treated patients with aneurysm, 2.46 times as great in those with aortic insufficiency and 2.06 times as great for the whole group. The duration of life from the onset of symptoms for the patients who died was found to be 1.47 times as great in the well treated as in the poorly treated patients for the whole group, 1.71 times as great in those with aneurysm and 1.37 times as great in the patients with aortic insufficiency. The importance of adequate treatment in cases of cardiovascular syphilis requires no comment.

Blackman<sup>37</sup> stated that while slight scarring along the edge of the mitral valve is not uncommonly found when syphilitic lesions of the

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36 Padget, P., and Moore, J. E. Results of Treatment in Cardiovascular Syphilis. Report of Three Years' Additional Observation, *Am Heart J* **10** 1017, 1935.

37 Blackman, S. S., Jr. Syphilis of the Mitral Valve and Membranous Interventricular Septum of the Heart, *Bull Johns Hopkins Hosp* **57** 111, 1935.

aortic valve are extensive, he has found only 1 report of a marked syphilitic lesion of the mitral valve. He described 2 additional cases in detail in which lesions of the mitral valve and membranous interventricular septum were directly continuous with syphilitic changes in the root of the aorta and aortic valves. Mitral lesions were suspected clinically in both cases in addition to aortic valvular disease.

Norris<sup>38</sup> found only 2 instances of syphilitic aortitis, presumably of congenital origin, in 14,000 autopsies performed at the Johns Hopkins Hospital. He pointed out that in order to prove without doubt that the condition in a certain case represents a congenital infection it is necessary to show that the patient's mother unquestionably had syphilis at the time of the child's birth and that the patient had other lesions of congenital syphilis or was known to have had a positive Wassermann reaction at an early age. However, in view of the great rarity of superinfection, it is reasonable to consider syphilitic aortitis with other manifestations of a congenital infection as being congenital. One of the author's cases occurred in a girl aged 9 years and the other in a youth aged 17. Both patients died suddenly, and necropsy revealed syphilitic aortitis and narrowing or occlusion of the coronary aorta.

Among 3,000 patients admitted to the wards of the medical service of the Baltimore City Hospitals there were 20, all under 46 years of age, suffering from marked cardiac decompensation unexplained by any of the usually accepted causes of heart disease<sup>39</sup>. All had positive Wassermann reactions. Five of the 20 died and were examined post mortem, and in none was any coronary sclerosis or valvular disease found. Microscopically, all showed extensive scarring and round cell infiltration of the myocardium. There was no sclerosis of the vessels of the kidneys, adrenal glands or other organs to suggest the possibility that a previous hypertension had existed. Magill suggested the possibility of syphilitic myocarditis.

#### MISCELLANEOUS INFECTIONS

Some years ago the important observations were made by Lewis and Grant that of an unselected series of patients with subacute bacterial endocarditis about one fourth present a congenitally bicuspid condition of the aortic valves and that about one fourth of those reaching adult life and having bicuspid aortic valves die of active endocarditis. Lewis and Grant necessarily concluded that the invasion of the blood stream by *Streptococcus viridans* is a common event, which in normal persons

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38 Norris, Robert F. Syphilitic Aortitis in Childhood and Youth. Report of Two Cases with Sudden Death, *Bull. Johns Hopkins Hosp.* **57**: 206, 1935.

39 Magill, T. P. Syphilitic Myocarditis, *Bull. Johns Hopkins Hosp.* **57**: 22, 1935.

is without evil results Okell and Elliott<sup>40</sup> sought to determine, by direct observation, the frequency with which *Str viridans* enters the blood stream of the average person They expressed the belief that this organism is found chiefly in the mouth and most frequently in cases of infection of the gums and that it is found elsewhere only in small numbers and under exceptional conditions They found a streptococcic bacteremia in 10.9 per cent of a group of persons with infected mouths Shortly after the extraction of teeth from obviously infected mouths a transient streptococcic bacteremia lasting a few minutes occurred in three fourths of their patients In persons without obvious disease of the gums, extraction of teeth was followed by a transient bacteremia in about one third of the patients These observations were based on the examination of the blood on a single occasion, and the organisms isolated from the blood were usually streptococci (*Str viridans*) which were culturally and serologically similar to strains obtained from the mouth This observation points to the importance of early prophylactic care of the teeth and gums, particularly in children with rheumatic or congenital heart disease

Von Glahn and Pappenheimer,<sup>41</sup> from pathologic observations on a series of 26 consecutive cases of subacute bacterial endocarditis, reached the opinion "that active rheumatic vegetations are, in persons who have had rheumatism, a necessary and practically constant prerequisite for the implantation of the bacteria" They summarized the evidence for this conclusion as follows

1 Vegetations histologically identical with those in rheumatic endocarditis and not containing bacteria are found (a) on the same valve as the bacterial vegetations, (b) on other valves on which there are no vegetations containing bacteria and (c) on the auricular wall

2 Aschoff bodies in the myocardium that are taken to indicate active rheumatic disease are found in practically the same proportion of cases of subacute bacterial endocarditis as of uncomplicated rheumatic cardiac disease

3 Types of bacterial endocarditis other than that due to nonhemolytic streptococci may be engrafted on active rheumatic vegetations This is a cogent argument against the view that the two types of lesions are a response of different intensity to the same infective agent, unless we dispense with current views as to the histologic specificity of the rheumatic reaction

They mightly emphasized that bacterial infection of the valves is not always the result of implantation on unhealed rheumatic lesions Furthermore, there may be added the possibility that a recrudescence of rheumatic fever may occur after subacute bacterial infection which

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40 Okell, C. C., and Elliott, S. D. Bacteraemia and Oral Sepsis with Special Reference to the Aetiology of Subacute Endocarditis, *Lancet* 2: 869, 1935

41 Von Glahn, W. C., and Pappenheimer, A. M. Relationship Between Rheumatic and Subacute Bacterial Endocarditis, *Arch Int Med* 55: 173 (Feb) 1935

was superimposed on a healed rheumatic lesion. This would equally well explain the association of active rheumatic carditis and subacute bacterial endocarditis.

Baker<sup>42</sup> has reviewed the subject of endocardial tuberculosis and added his own observations. Tuberculous endocarditis was found 6 times in about 900 consecutive necropsies at Duke Hospital. In 5 instances there were small scattered tubercles occurring on all parts of the endocardium as part of a generalized miliary infection. In one instance the endocardial process resulted from the extension of pericardial and myocardial tuberculosis through the cardiac wall. Baker expressed the belief that the tubercles probably arise by implantation via the blood stream, but endocardial lesions may also develop by extension from the myocardium. A critical survey of reported cases of tuberculous endocarditis as a diffuse process at the line of closure of the valves reveals only 1 case in which the diagnosis is probably correct. The toxic action of a tuberculous process somewhere in the body does not result in sclerosis of the endocardium or healed fibrous or calcified valvular lesions.

In the past three years Spink<sup>43</sup> has observed 35 sporadic cases of trichinosis. Although clinical evidence of myocardial damage was present in only 1 case, abnormal electrocardiographic changes were noted in 6 of the 18 cases in which this test was performed. The electrocardiographic abnormalities included changes in the T wave and low amplitude and abnormal duration of the QRS complex. Spink expressed the belief that the acute myocarditis occurring in cases of trichinosis may be a nonspecific inflammatory reaction due to the invasion of the myocardium by larvae.

#### THE HEART IN THYROID DISEASE

Nahum and Hoff<sup>21</sup> injected 50 mg of acetyl- $\beta$ -methylcholine chloride into a patient with hyperthyroidism suffering from auricular flutter with 2:1 block. Gradually the block increased to 4:1 and then to 5:1, and soon auricular fibrillation supervened. An hour and a half later, when the effect of the injection could be expected to have worn off, a normal slow supraventricular rhythm spontaneously reappeared.

Stimulated by this interesting observation, Nahum and Hoff sought to discover whether acetyl- $\beta$ -methylcholine chloride might play a similar rôle in converting the normal heart mechanism in patients with hyperthyroidism into auricular fibrillation. Accordingly 5 patients with normal cardiac rhythm were given 0.75 mg of the drug per kilogram of body weight, and continuous electrocardiograms were made. In 4

42 Baker, R. D. Endocardial Tuberculosis, *Arch. Path.* **19**: 611 (May) 1935.

43 Spink, Wesley W. Cardiovascular Complications of Trichinosis, *Arch. Int. Med.* **56**: 238 (Aug.) 1935.

patients definitely suffering from hyperthyroidism short periods of auricular fibrillation appeared, but this was not observed in 1 patient with doubtful hyperthyroidism. The normal cardiac mechanism reappeared from five to twenty minutes later. Since the acetylcholine derivative reproduces the same effects on the pacemaker and auricle of the heart as stimulation of the vagus nerves, Nahum and Hoff concluded that one factor in the spontaneous production of auricular fibrillation is the action of the vagus nerves on the heart. However, the failure to produce auricular fibrillation in normal persons with the same or even with larger doses of the drug makes it seem obvious that thyroxine is an additional factor which acts with the vagus nerve. The widespread occurrence of auricular fibrillation in persons not suffering from hyperthyroidism indicates that agents other than thyroxine may operate with the vagus factor to induce and maintain this disorder. The authors found that in cats electric shock may produce auricular fibrillation when acting with the vagus factor. It is suggested that in cases of mitral stenosis stretching or inflammation of the auricle in cases of hypertension vagal overactivity and in cases of congestive failure distention of the auricle may be a significant factor.

On the basis of their own studies and of those reported by other investigators, Boothby and Rynearson<sup>44</sup> showed that the increase in the circulatory rate in patients with exophthalmic goiter who are not treated with iodine is much greater than that which occurs in normal persons as the result of an increase in oxygen consumption due to work. The same is true in lesser degree for patients receiving iodine treatment. These facts suggest to the authors the hypothesis that in persons with exophthalmic goiter there is a peculiar circulatory stimulant which causes a greater increase of the circulatory rate than occurs in a normal subject as a result of a corresponding increase in oxygen consumption. After effective iodine medication this stimulant is decreased in amount or its effectiveness is lessened.

There have been a number of interesting clinical reports<sup>45</sup> concerning various phases of the relationship between the heart and thyroid disease, a few are mentioned by title

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44 Boothby, Walter M. and Rynearson, Edward H. Increase in Circulation Rate Produced by Exophthalmic Goiter Compared with That Produced in Normal Subjects by Work, *Arch Int Med* **55** 547 (April) 1935

45 Viethen, A. Herzverengung bei Morbus Basedow in Kindern, *Monatsbl f Kinderh* **64** 81, 1935. Margohes, A., Rose, E., and Wood, F. C. The Heart in Thyroid Disease. I The Effect of Thyroidectomy on the Orthodiagram. *J Clin Investigation* **14** 483 1935. Rose, E., Wood, F. C., and Margohes, A. The Heart in Thyroid Disease. II The Effect of Thyroidectomy on the Electrocardiogram, *ibid* **14** 497, 1935. Sise, L. F. Anesthesia for Thyrocardiac Patients, *J A M A* **105** 1662 (Nov 23) 1935. Parade, G. W. Relative Aorteninsuffizienz bei Morbus Basedow. *Deutsche med Wchnschr* **61**-1799, 1935. Wiechmann, E. Relative Aorteninsuffizienz bei Basedow, *ibid* **61**-10, 1935.

## PERICARDIAL DISEASE

Chronic constrictive pericarditis, commonly called Pick's disease, may be cured by surgical means. This fact has stimulated much interest in the disease,<sup>46</sup> and the comprehensive clinical report by White<sup>47</sup> may be profitably reviewed.

He defined chronic constrictive pericarditis as a

chronic fibrous or callous thickening of the wall of the pericardial sac which is so contracted that the normal diastolic filling of the heart is prevented. A condition called "inflow stasis" results. There may or may not be calcification of the pericardium, obliteration of the pericardial cavity, or important external pericardial adhesions. There may or may not be an associated accumulation of pericardial fluid in small amounts, as in pockets. The parietal pericardium may be preponderantly affected or the epicardium also seriously involved, or both pericardial membranes may be securely or even inseparably united. One section of the pericardium, as over the cardiac apex, may remain relatively free and but slightly thickened, while the other part, as over the right auricle and great veins, is markedly contracted, or the entire heart and roots of the great vessels may be encased uniformly in a tightly fitting envelope. There may or may not be an acute or chronic polyserositis, which is, contrary to a common belief, a different thing. There may or may not be frosted liver or spleen. There may or may not be heart disease itself—the association of chronic constrictive pericarditis, of any important degree at least, with heart disease is very rare.

From a study of 15 cases, which are reported in detail, it is emphasized that in diagnosis

one should take into consideration not only individual signs alone but the entire clinical picture and history of the case. The leading clues are the result of "inflow stasis," namely (1) the insidious onset of dropsy in a young person, (2) preponderant liver enlargement and ascites, (3) increased prominence of the jugular veins, (4) normal or relatively normal heart in the presence of dropsy without nephritis, and (5) low blood and pulse pressure and paradoxical pulse. Other important clues are (6) X-ray evidence (poor pulsation, calcification, chronic pleuritis), (7) electrocardiographic abnormalities (low voltage or "coronary" T waves in chronic disease in early youth), and (8) a previous history of acute pericarditis or polyserositis.

Chronic constrictive pericarditis has been confused with four other conditions, but with ordinary care and thought such errors of diagnosis should not arise. The four conditions are mitral stenosis, polyserositis (including instances of perihepatitis or frosted or iced liver—Zuckergussleber), primary cirrhosis of the liver, and nutritional oedema. Two other conditions—namely, tricuspid stenosis and mediastinal tumors—may also cause some of the same signs.

The prognosis of cases with chronic constrictive pericarditis for good health is poor unless suitable for, and submitted to operation, although mild or only

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46 Burwell, C. S., and Flickinger, D. Obstructing Pericarditis. Effect of Resection of the Pericardium on the Circulation of a Patient with Concretio Cordis, *Arch Int Med* **56** 250 (Aug.) 1935. Winkelbauer, A., and Schur, M. Surgical Therapy of Adherent Pericarditis, *Med Klin* **31** 1269, 1935. Beck, C. S. Two Cardiac Compression Triads, *J A M A* **104** 714 (March 2) 1935.

47 White, P. D. Chronic Constrictive Pericarditis (Pick's Disease) Treated by Pericardial Resection, *Lancet* **2** 539 (Sept. 7), 597 (Sept. 14) 1935.



moderately severe cases may live for many years a semi-invalid requiring much rest and frequent or occasional abdominal paracenteses

Cure is now possible by surgery and an imposing number of successful cases of pericardial resection (by the Delorme operation, and not by that proposed by Brauer) is being accumulated. In our own clinic twelve cases have had this operation performed, ten by one surgeon, of these latter ten cases, six have been completely cured and one other relieved to a high degree. The first successful case in America, operated on seven years ago in 1928, belongs to this group, this patient, a young woman, is in excellent health to-day, as are the other five cases of complete cure.

Nothing of especial importance or interest has been published on acute pericarditis.

#### CARDIAC TRAUMA

Bright and Beck<sup>48</sup> have made an interesting and important study of wounds of the heart produced by contusive or compressive forces. They expressed the belief that the thoracic cage by no means perfectly protects the heart and that this organ is the recipient of many injuries, which are rarely recognized. The heart, lying against the sternum, is vulnerable to any sudden impact over the sternum and, buttressed against the bodies of the thoracic vertebrae posteriorly, is vulnerable to compression forces applied to the chest.

They have comprehensively reviewed and analyzed the medical literature pertaining to nonpenetrating cardiac wounds and classified the various ways in which such wounds may be produced.

I A direct blow over the precordium producing fracture of sternum or ribs, the broken ends of which are driven into the heart.

II Contusion or compression of the heart between the sternum anteriorly and the vertebrae posteriorly.

III The application of indirect forces, such as by the sudden compression of the legs and abdomen.

IV Laceration of the thoracic viscera, such as may be sustained in a fall from a high building.

V Concussion of the heart.

In the analysis of 175 cases they found that when the heart receives a contusion the result may be (1) rupture of the heart (152 instances), (2) myocardial failure without rupture (11 instances), or (3) recovery (12 instances). It is pointed out that these proportions do not represent the correct relative incidence of these three types of sequelae to contusion because many patients recover without the correct diagnosis having been made. In a consideration of the 152 cases of rupture of the heart, it was found that the four cardiac chambers seem to be equally vulnerable. The right auricle was ruptured in 36 cases the left

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<sup>48</sup> Bright, E. F., and Beck, C. S. Nonpenetrating Wounds of the Heart. A Clinical and Experimental Study, *Am Heart J* **10** 293, 1935.

auricle in 30, the right ventricle in 31 and the left ventricle in 37. More than one chamber was ruptured in 13 cases. The chief clinical manifestations were those of sudden collapse. Some patients complained of precordial pain, or the pain was referred to the heart, to the left side or to the shoulder. The pulse was either slow or rapid, but as the pressure in the pericardial cavity increased, the pulse became feeble. Vomiting and headache sometimes occurred. In some patients restlessness, anxiety and air hunger developed. The cardiac sounds became distant and even inaudible. As the blood pressure fell, the skin became cold and blanched, and finally unconsciousness supervened.

In the majority of patients in this group death was due to hemo-cardiac tamponade. In the group of 152 patients death occurred immediately after the accident in 47, 42 survived for a period the length of which was not mentioned, but the interval was undoubtedly short. Only a few patients survived more than two weeks, and these died within two months.

In regard to treatment, the authors expressed the opinion that in the group of 152 cases there were 30 in which it seemed that operation offered some chance of success. The operative treatment is discussed.

In order to study better the effect of contusions on the heart, Bright and Beck performed a series of 25 experiments on dogs by exposing the heart and applying contusive injuries to the myocardium. When the right or left ventricle was struck a number of blows, the heart rate became rapid, the myocardium became swollen from hemorrhage, usually there was some dilatation and not infrequently a hemorrhagic effusion developed. The electrocardiogram showed changes similar to those observed in disease of the coronary arteries. Although it appeared as if softening and rupture would surely follow, death occurred in only 5 instances. The cause of death was rupture in 1 instance, ventricular fibrillation in 2 and myocardial failure in 2.

On the basis of their experimental study the authors concluded that the heart can tolerate a great amount of trauma and that rupture is a rare complication. They expressed the belief that the vast majority of nonpenetrating wounds of the heart are not recognized clinically. The patients recover, and as the correct clinical diagnosis is not usually made their cases do not find the way into medical reports.

#### PULMONARY DISEASE AND THE HEART

Brenner<sup>49</sup> has written a comprehensive treatise on the pathology of the vessels of the pulmonary circulation based on a study of the

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<sup>49</sup> Brenner, O. Pathology of the Vessels of the Pulmonary Circulation I, II, III, IV and V, *Arch Int Med* 56 211 (Aug), 457 (Sept), 724 (Oct); 976 (Nov), 1189 (Dec) 1935.

results of 100 consecutive unselected autopsies, the paper is one which any person especially interested in this field may profitably read

The immediate effect of a high degree of occlusion of the pulmonary artery on the heart results in a condition which McGinn and White<sup>50</sup> have termed "acute cor pulmonale" Nine cases of the condition, in which it resulted from pulmonary embolism, are reviewed in detail and summarized as follows

2 The symptoms and signs of extensive pulmonary embolism are variable, but predominating at first are those of shock—namely, collapse, pallor, sweating, apprehension, and a fall in blood pressure—to be followed by reaction to the infarction itself—namely, fever and elevation of the pulse and respiratory rates In none of our cases did we find acute chest pain in the absence of pleural involvement, but most of the patients complained of substernal oppression and suffocation Respiratory distress was marked in all cases

3 If the state of shock from extensive pulmonary embolism is not too great, or after it has largely cleared, there may be found signs indicative of the secondary effect of the pulmonary embolism on the heart itself that is, the acute cor pulmonale (dilatation of the right chambers) attended by pulmonary artery dilatation Auscultation in our cases frequently showed accentuation of the pulmonary second sound, gallop rhythm heard best in and just below the pulmonary valve region, and in two cases a "pericardial" friction rub with maximal intensity in the region of the second, third and fourth interspaces Cyanosis and engorgement of the neck veins were common manifestations at some time during the attack These changes remained for only a short period in some cases Pleural friction rubs were heard frequently

4 Electrocardiograms taken soon after the occurrence of the pulmonary embolism showed similar changes in five of our patients, and in two others taken some time after the attack they had some of the characteristics, although they were less definite The changes that appear significant are the presence of a Q wave and late inversion of the T wave in lead 3, the rather low origin of the T wave with a gradual staircase ascent of the ST interval in lead 2, a prominent S wave and a slightly low origin of the T wave in lead 1, and an upright T wave (with inverted P and QRS waves) in lead 4 In none of our cases was left axis deviation present at any time of the acute episode, whereas the tracings of two patients showed definite right axis deviation

Electrocardiograms of two patients taken after recovery showed a complete disappearance of the changes already mentioned, and in a third patient there was almost a complete disappearance of abnormalities in a record taken forty-eight hours after the attack and twenty-seven hours after the first electrocardiogram All three of these cases showed a change in the axis deviation, one had a prolonged PR interval, and in one case in lead 4 the T wave was reverting to normal (inverted) Our follow-up studies indicate that the electrocardiographic changes are temporary and may disappear within forty-eight hours after the attack of pulmonary embolism

5 It is probable that the changes observed clinically and the electrocardiographic variations in cases showing the acute cor pulmonale consequent on pul-

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50 McGinn, Sylvester, and White, Paul D Acute Cor Pulmonale Resulting from Pulmonary Embolism Its Clinical Recognition, *J A M A* **104** 1473 (April 27) 1935

monary embolism are due in large part to dilatation and partial failure of the chambers of the right side of the heart .

Air embolism <sup>51</sup> is an uncommon but extremely interesting disorder. Different mechanisms have been suggested as being responsible for death, namely, cerebral or coronary air embolism or suffocation from obstruction of the pulmonary artery. If air is injected into a systemic vein, it collects in the pulmonary artery and its branches and does not accumulate in the heart or elsewhere until the volume injected exceeds the volume of the pulmonary artery and its branches. Consequently large amounts are well tolerated before suffocation occurs. However as little as 1 cc. of air introduced into one of the pulmonary veins may cause fatal coronary or cerebral embolism. It is only natural therefore, that surgeons who operate on the chest and those employing pneumothorax therapy encounter this complication more frequently than others. The clinical picture of coronary air embolism is variable but it is usually that of severe shock. The electrocardiogram may show changes similar to those seen in cases of coronary infarction.

#### SYNCOPE

Weiss <sup>52</sup> has written an excellent authoritative account of syncope and related syndromes. The various types of syncope are separated according to the underlying physiologic mechanism so far as that is possible. Incidence, pathogenesis, clinical manifestations and treatment of the several types are considered.

Ferris, Capps and Weiss <sup>53</sup> have sought to clarify the mechanism involved in the so-called "cerebral type" of syncope due to involvement of the carotid sinus. This form of syncope occurs spontaneously and can be reproduced in susceptible persons, it results not from bradycardia or a fall in blood pressure but apparently from some reflex action on the central nervous system. Extensive studies on 32 patients permitted the authors to reach important conclusions. Of particular interest in this connection is the fact that digitalis has been found to have a sensitizing effect not only on the usual carotid sinus reflex but also on the carotid sinus cerebral reflex. The authors expressed the belief that this possi-

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51 Wolffe, J. B., and Robertson, H. F. Experimental Air Embolism, *Ann Int Med* 9 162, 1935. Durant, T. M. The Occurrence of Coronary Air Embolism in Artificial Pneumothorax, *ibid* 8 1625, 1935.

52 Weiss, S. Syncope and Related Syndromes, in Christian, Henry A., and Mackenzie, J. Oxford Medicine, New York Oxford University Press, 1929, vol 3, pt 1, p 250.

53 Ferris, E. B., Capps, R. B., and Weiss, S. Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions. *Medicine* 14 377, 1935.

bility must be kept in mind when digitalizing elderly patients, as it may cause not only powerful cardiac inhibition but also vasomotor depression

#### ARTERIAL HYPERTENSION

The interdependence between renal function in its widest meaning and arterial hypertension is being studied by several groups of investigators in different countries. The published results are extremely discordant but are of great interest because of the importance of the problem. Many workers, especially in America and in England, have been busy merely disproving the claims and theories of other investigators.

It has been shown that arterial hypertension can be experimentally produced by various procedures which injure the kidney, such as destroying or removing a considerable portion of the renal tissue or reducing the blood flow by compression of the renal artery. It has been suggested that the hypertension so produced may be due to failure in the excretion of certain pressor substances in the blood, to interference with the elaboration of certain pressor or depressor "hormones" or to reflex action on the vasomotor center.

It has been claimed, furthermore, that experimental hypertension brought on by the injection of kaolin into the cisterna magna or by denervating the carotid sinus and cutting the depressor nerves is dependent on the intact nerve supply to the kidneys. Thus in dogs in which the blood pressure is raised as a result of injection of kaolin the pressure is said to fall if one kidney is denervated but to rise again if the denervated kidney is removed.

Braun and Samet<sup>54</sup> presented protocols of experiments on dogs whereby increased arterial blood pressure was produced either by injection of kaolin or by cutting depressor nerves. The hypertension was quickly abolished after denervation of one or both kidneys, whereas the denervation of other vascular areas was without effect. Also, preliminary denervation of the kidneys prevented any rise in blood pressure.

Pick<sup>55</sup> produced experimental hypertension in dogs by injecting kaolin into the cisterna magna and then found that 20 cc of blood from one of these animals injected into a normal dog raised its blood pressure for several days. However, this rise of blood pressure in the second dog could be abolished by injecting 20 cc of blood from a dog after the kidneys had been denervated. Pick expressed his intention

54 Braun, L., and Samet, B. Experimentelle Untersuchungen über die Beziehungen zwischen Blutdruck und Niere, *Arch f exper Path u Pharmacol* **177** 662, 1935

55 Pick, E. P. Ueber humorale Uebertragung hohen und niedrigen Blutdrucks, *Wien klin Wchnschr* **48** 635, 1935

to investigate further the mechanism involved, including the possibility of depressor hormones being elaborated by a denervated kidney

Page<sup>56</sup> has investigated the suggestion that elevation of blood pressure associated with either inflammatory or vascular disease of the kidneys may be due to nervous impulses originating in the kidneys and conducted by way of the extrinsic renal nerves to the vasomotor centers. He found that the hypertension produced in dogs by constricting the renal arteries or by irradiating the kidneys was not affected by preliminary stripping of the renal pedicle of its extrinsic nerve supply. He concluded that these nerves do not appear to participate in the genesis of renal hypertension, at least of these types. Hypertension produced by constriction of the renal arteries did not cause significant changes in renal efficiency.

Acting on the supposition that the unknown cause of essential hypertension may lie in nervous impulses from the kidney, Page and Heuer<sup>57</sup> performed bilateral denervation of the kidney on a patient with essential hypertension uncomplicated by detectable renal involvement. No change in the level of arterial blood pressure resulted, and consequently there was no support for the hypothesis underlying the procedure. No ill effects, either renal or extrarenal, were observed after the denervation.

The hypothesis of Volhard that hypertension of renal origin is caused by pressor substances circulating in the blood has received apparent experimental support from workers in his laboratory and elsewhere. The evidence on which this hypothesis rests has naturally been subjected to critical repetition by many investigators, and during the past year careful studies have been reported,<sup>58</sup> which have in common the conclusion that there is no increase in pressor substances in the blood of patients with hypertension of any type.

This whole problem of essential hypertension and hypertension in relation to renal disease is still unsettled. New theories are advanced faster than old ones can be disproved. The recent experimental studies are extremely interesting, and it is of the greatest significance that

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56 Page, Irvine H. The Relationship of the Extrinsic Renal Nerves to the Origin of Experimental Hypertension, *Am J Physiol* **112** 166, 1935.

57 Page, Irvine H., and Heuer, George J. The Effect of Renal Denervation on the Level of Arterial Blood Pressure and Renal Function in Essential Hypertension, *J Clin Investigation* **14** 27, 1935.

58 Aitken, R. S., and Wilson, C. An Attempt to Demonstrate a Pressor Substance in the Blood in Malignant Hypertension, *Quart J Med* **4** 179, 1935. Capps, R. B., Ferris, E. B., Jr., Taylor, F. H. L., and Weiss, Soma. Role of Pressor Substances in Arterial Hypertension, *Arch Int Med* **56** 864 (Nov.) 1935. Page, Irvine H. Pressor Substances from the Body Fluids of Man in Health and Disease, *J Exper Med* **61** 67, 1935.

permanent arterial hypertension, obviously of renal origin, can be produced in dogs without there being significant evidence of renal insufficiency

#### CORONARY ARTERIOSCLEROSIS

For nearly thirty years it has been known that the feeding of cholesterol or of foods rich in cholesterol results in the development of widespread lesions of the arteries in rabbits. The similarity between these lesions and the lesions typical of human arteriosclerosis stimulated immensely the study of experimental arteriosclerosis caused by cholesterol, and the results of this study have been applied directly to man by many investigators. Duff<sup>59</sup> has critically examined the entire problem with the purpose of determining what facts have been established and of evaluating their importance as applied to the solution of problems of arteriosclerosis in man. It is distinctly worth while to review his paper in some detail.

When rabbits have been given cholesterol for some time, lesions of the arteries appear. The first lesions appear in the arch of the aorta about the mouths of the vessels arising from it or just above the aortic valve ring. Lesions appear later in other portions of the aorta and its larger branches, and finally the smaller branches may show nodular lesions. The coronary arteries are often attacked. The nature of the lesions seems to be essentially the same wherever they occur. The first visible alteration is a swelling of the ground substance, which is normally a thin layer separating the lining endothelium from the internal elastic lamina. Here the deposition of lipoids may become abundant, and it seems probable that they consist chiefly of cholesterol and its esters. These deposits stir into activity numerous macrophages, which are attracted to the site and which then engulf a large part of the lipid material. With the development of the lesions, necrotic areas appear, and there is extensive fibroblastic proliferation. Medial lesions occur and may be independent of intimal lesions, although they are commonly associated with them. After the administration of cholesterol is discontinued, the arterial lesions are found to persist to the end of the longest experiments, but they show evidence of transition toward a more fibrous type.

The method of cholesterol feeding has been applied to a variety of experimental animals other than rabbits. Although arterial lesions have been produced with difficulty in guinea-pigs, there has been no convincing demonstration of a similar effect in any other animal. Intensive and prolonged feeding of cholesterol does not affect in any way the arteries of cats, dogs, foxes or monkeys. It is interesting to consider

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59 Duff, G. Lyman. Experimental Cholesterol Arteriosclerosis and Its Relationship to Human Arteriosclerosis, *Arch. Path.* 20: 81 (July), 259 (Aug.) 1935

further various factors influencing the development of cholesterol-induced arteriosclerosis in the rabbit

Whereas the continued feeding of cholesterol is incapable of producing any striking sustained rise in the cholesterol content of the blood in animals such as dogs, in rabbits, on the contrary, the cholesterol content of the blood is raised to many times the normal value. This is probably because the mechanism for handling exogenous cholesterol is amply sufficient in animals such as dogs, whereas it is deficient in rabbits.

Certain facts, however, have suggested that some factor in addition to cholesterol feeding with resulting hypercholesteremia is necessary or important to the development of the arterial lesions. Hypercholesteremia, for example, may develop in the rabbit without producing any changes in the arteries within the usual experimental period. Furthermore, the patchy distribution of the lesions when they are produced suggests some preceding local condition in the involved areas which favors the precipitation of lipoids.

The question of the possible influence of rises in blood pressure has been considered, but there is no satisfactory evidence to show that an increase in blood pressure can affect the progress of the arterial lesions.

Of especial interest is the fact that extirpation of the thyroid gland has been found to facilitate the development of the lesions without significantly affecting the curve for cholesterol content of the blood. The feeding of thyroid extract in conjunction with cholesterol retards the progress of the lesions, but in animals receiving that mixed regimen the resulting hypercholesteremia is much less extreme than that which occurs in control animals fed cholesterol alone. It has been further shown that large doses of organic iodine compounds or of potassium iodide retard or even prevent the development of experimental cholesterol-induced arteriosclerosis in rabbits, owing apparently to the fact that the administration of the iodine greatly diminishes the hypercholesteremia, although this explanation is not accepted by all observers.<sup>60</sup> The possibility that the iodine compounds act through an influence on thyroid activity has been shown to be the case, for the prophylactic effect is abolished by thyroidectomy. It has been shown recently<sup>61</sup> that iodine has no influence on the involution of vascular lesions previously produced by the feeding of cholesterol.

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<sup>60</sup> Page, I. H., and Bernhard, W. G. Cholesterol-Induced Atherosclerosis: Its Prevention in Rabbits by the Feeding of an Organic Iodine Compound, *Arch Path* **19** 530 (April) 1935.

<sup>61</sup> Meeker, D. R., Kesten, H. D., and Jobling, J. W. Effect of Iodine on Cholesterol-Induced Atherosclerosis, *Arch Path* **20** 337 (Sept.) 1935.



Various noxious agents which have in common the ability to injure the arterial walls have been shown to facilitate the development of arterial lesions, among those tested have been mechanical injury, nicotine, epinephrine, viosterol and bacteria

It may be safely concluded that in rabbits hypercholesteremia is a necessary prerequisite for the formation of lipid deposits in the arterial walls, but in addition some unknown factor inherent in the experimental procedure produces an injury to the walls of the arteries. This injury is responsible for the local histologic changes which precede the appearance of lipid deposits and is essential for their deposition.

Of chief concern are the significance of the aforementioned experimental data in regard to the etiology of human arteriosclerosis. Certain important differences between man and the rabbit in this connection may be pointed out.

Although the anatomic lesions, especially the intimal lesions, of experimental arteriosclerosis are similar to those of the disease in man, important differences are noted, especially in regard to the distribution of lesions, and the medial sclerosis which may be a feature in the early stages of the disease in rabbits. These and other differences between the two types of lesions require caution against the hasty conclusion that their etiology is identical or that etiologic factors which may be common to them must operate with equal intensity in the two instances.

Three main factors seem implicated in the production of the lesions in rabbits, namely, the cholesterol-rich diet, hypercholesteremia and the occurrence of injury to the arteries. Certain differences between the rabbit and man indicate that these factors do not operate in man in exactly the same way as in the rabbit.

The rabbit is a herbivorous animal, and vegetable diets are cholesterol-poor, man, on the contrary, is omnivorous, and varying quantities of cholesterol are contained in his normal diet. The rabbit excretes exogenous cholesterol with difficulty, and hypercholesteremia can be easily produced, in the case of man, however, large quantities of cholesterol in the diet have only a relatively slight and temporary effect on the level of cholesterol in the blood, owing to the ease with which cholesterol is excreted. The normal cholesterol content of human blood is approximately twice as great as that of rabbit's blood, and spontaneous arterial lesions are characterized in man by accumulations of lipoids, while in the rabbit no such accumulations occur. Elevation of the normal cholesterol level of the blood is necessary to the development of the fatty arterial lesions in rabbits, whereas in man hypercholesteremia is not found with any regularity in association with arteriosclerosis.

The occurrence of preliminary local alterations in the walls of human arteries before the formation of lipid deposits may be regarded as an established fact, and this is likewise an essential factor in the develop-

ment of the experimental lesion in the rabbit. Thus with respect to the primary local changes in the arterial walls, experimental cholesterol-induced arteriosclerosis in the rabbit may well be compared with arteriosclerosis in man. Many of the experimental measures which have been employed for the production of injury to the arteries of rabbits seem to have no direct significance as applied to man, owing to the fact that the arteries of rabbits are extraordinarily susceptible to injury, but this does not detract from the general conclusion that the local alterations leading to lipoid deposition are the result of some sort of injury.

Duff concluded that experiments on cholesterol feeding provide no valid reason for believing that a disturbance of cholesterol metabolism plays any part in the etiology of human arteriosclerosis. The cause of the arterial injury which initiates the development of human arteriosclerosis is obscure, and the experiments on cholesterol feeding provide hardly any suggestive information bearing on this most important problem.

We are inclined to agree with Duff, but needless to state there is a competent body of medical opinion which does not subscribe to his main conclusions. During the past year Leary<sup>62</sup> has again presented his arguments that atherosclerosis is a metabolic disease.

There have been a number of interesting clinical and experimental studies<sup>63</sup> relating to the coronary circulation, cardiac pain and myocardial infarction which, owing to considerations of space, cannot be reviewed.

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62 Leary, Timothy. Pathology of Coronary Sclerosis, *Am Heart J* **10** 328, 1935, Atherosclerosis. The Important Form of Arteriosclerosis, a Metabolic Disease, *J A M A* **105** 475 (Aug 17) 1935.

63 Green, Charles W. The Nerve Control of the Coronary Vessels with New Experimental Evidence for the Pathways of Efferent Constrictor and Dilator Neurones in the Dog, *Am J Physiol* **113** 361, 1935, Control of the Coronary Blood Flow by Reflexes Arising in Widely Distributed Regions of the Body, *ibid* **113** 399, 1935. Katz, L. N. Mechanism of Pain Production in Angina Pectoris, *Am Heart J* **10** 322, 1935. Katz, Louis N., Mayne, Walter, and Weinstein, William. Cardiac Pain. Presence of Pain Fibers in the Nerve Plexus Surrounding the Coronary Vessels, *Arch Int Med* **55** 760 (May) 1935. Kisch, F. Angina Pectoris im Arbeitstest, *Klin Wchnschr* **14** 1165, 1935. Leriche, R., and Fontaine. Contribution experimentale a l'etude de la circulation coronarienne chez l'animal entier. Le role du sympathique dans l'innervation des coronaires, *Ann de med* **37** 407, 1935. Nemet, G., and Gross, H. Interrelationship of Arteriosclerotic Heart Disease and Chronic Congestive Failure, *Am Heart J* **10** 643, 1935. Nuzum, F. R., Elliott, A. H., and Evans, R. D. A Clinical and Pathological Study of Coronary Sclerosis. Its Incidence in Hypertension and Angina Pectoris, *ibid* **10** 367, 1935. Robertson, Harold F. The Reestablishment of Cardiac Circulation During Progressive Coronary Occlusion, *ibid* **10** 533, 1935. Shambaugh, Philip. Circulatory Changes in Angina Pectoris. An Experimental Study, *Arch Int Med* **56** 59 (July) 1935. Tennant, R., and Wiggers, C. J. The Effect of Coronary Occlusion on Myocardial Contraction, *Am J Physiol* **112** 351 1935.

Of especial interest are the findings of Saphir and his co-workers<sup>64</sup> based on a study of 34 cases selected by a pathologist without previous knowledge of the clinical and electrocardiographic findings. After the anatomic material had been studied, the clinical and electrocardiographic records were reviewed, and the attempt was made to correlate the findings thus obtained with the anatomic lesions.

Both coronary arteries were found to be involved, and some degree of myocardial fibrosis was present in all hearts examined. The most severe lesions were found in the left coronary artery, especially in the descending branch. Myocardial infarcts were noted in 28 instances, and at least two branches of the coronary arteries supplying the infarcted areas were involved. In 4 hearts, infarcts were present without any occlusion of the coronary arteries, although their lumens were markedly narrowed. Such infarcts were probably caused by transient myocardial insufficiency, which in the presence of narrowed coronary arteries led to a temporarily inadequate blood flow.

Saphir and his co-workers found that the electrocardiogram may fail to give any clue to the full significance of previous clinical attacks and does not always aid in determining whether or not coronary thrombosis or myocardial infarction is present. Furthermore, it was not found possible to locate the position of the infarct from electrocardiographic records obtained with the standard three leads.

Pain referable to the heart occurred in only 18 of their 34 patients, but coronary thrombosis was encountered 32 times; there were only 4 instances in which an attack of pain unrelated to effort could reasonably be correlated with the occurrence of coronary thrombosis or myocardial infarction. On the other hand, coronary sclerosis and myocardial fibrosis alone were present in 4 instances at the time attacks of pain unrelated to obvious effort occurred. Saphir and his co-workers found the duration and severity of pain to be unreliable guides in diagnosing coronary thrombosis.

Not coronary thrombosis nor myocardial infarction nor coronary arteriosclerotic occlusion can be the anatomical equivalent of angina pectoris because these lesions were found not only in the presence of angina pectoris but also in patients who never had attacks of angina pectoris. Besides, these lesions were not constantly present in hearts of patients dying following attacks of angina pectoris. Only one anatomical change was common to all hearts of patients who had attacks of angina pectoris, namely, coronary sclerosis and myocardial fibrosis. To the morphologist, coronary sclerosis and fibrosis of the heart mean a labile myocardium which may fail suddenly. It seems that the sudden failure, or the subsequent events, is intricately linked with anginal attack in some manner as yet undetermined.

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64 Saphir, O. Priest, W. S., Hamburger, W. W., and Katz, L. N. Coronary Arteriosclerosis, Coronary Thrombosis and the Resulting Myocardial Changes, *Am Heart J* 10 567 (June), 762 (Aug.) 1935.

In the present state of our knowledge, it appears impossible to differentiate clinically between myocardial infarction brought about by coronary thrombosis and that following arteriosclerotic narrowing or occlusion of the coronary arteries. It is also difficult to determine the occurrence of coronary thrombosis and myocardial infarction clinically, either because the thrombosis and infarct may occur "silently," or because the characteristic picture may be found in the absence of thrombosis and infarction.

Beck and his associates<sup>65</sup> have concerned themselves for some time with the problem of increasing the blood supply to the heart by operation. Their first studies were made on dogs in which the epicardium and the lining of the parietal pericardium of the heart were removed and adhesions were allowed to form between the myocardium and the vascular bed afforded by the parietal pericardium and pericardial fat. A pressure differential was found necessary to promote anastomosis between the cardiac and the extracardiac vascular bed, which was provided by reducing the normal coronary blood supply. After the establishment of the collateral circulation it was found possible to reduce greatly the lumen of the right or left coronary artery near the aorta without fatally injuring the heart.

Further experiments were carried out, in which pedicle grafts of muscle together with the pericardial and mediastinal fat were used for the vascular bed. Anastomoses readily developed between skeletal and cardiac muscle if a sufficient pressure differential was provided. When the collateral vascular supply was well established it was possible to ligate the right coronary artery or the descending branch of the left coronary artery without producing a fatal injury, provided the ligation was carried out in two stages. From a clinicopathologic study of human material it was judged that nearly half of the patients would have been suitable subjects for operation and might have benefited by the production of the extracardiac collateral circulation. Pedicle grafts of pectoral muscle were sutured to the circumflex region of the heart in more than 6 patients with heart disease with involvement of the coronary arteries. The results have been sufficiently encouraging to justify further exploitation of this important problem.

Forty patients with angina pectoris have been treated neurosurgically by White<sup>66</sup> for the relief of pain which did not respond to medical treatment. Surgical excision of the upper thoracic ganglions has given

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<sup>65</sup> Beck, Claude S. The Development of a New Blood Supply to the Heart by Operation, *Ann Surg* **102** 801, 1935. Beck, C. S., and Tichy, V. L. The Production of a Collateral Circulation to the Heart. An Experimental Study, *Am Heart J* **10** 849, 1935. Moritz, A. R., and Beck, C. S. The Production of a Collateral Circulation to the Heart. Pathological Anatomical Study, *ibid* **10** 874, 1935.

<sup>66</sup> White, J. C. The Autonomic Nervous System, New York, The Macmillan Company, 1935.

nearly perfect relief on the side on which operation was performed, but the procedure was found to be too dangerous. White has found the paravertebral injection of alcohol, on the other hand, to be a reasonably safe procedure. It gave excellent results in 67.7 per cent of the cases, and converted the severe forms of angina pectoris into milder types which could be more easily controlled by medical measures in another 17.6 per cent. In the remaining 14.7 per cent of cases pain was not satisfactorily relieved, but in each instance the signs of paralysis of the sympathetic nerves and complete anesthesia of the intercostal nerves was not produced. The technic and complications of paravertebral injection of alcohol are discussed.

There has been further evidence<sup>67</sup> of the beneficial effect of theophylline ethylene-di-amine in the treatment of heart disease with involvement of the coronary arteries. It was shown that this drug promotes the development of the collateral circulation in cases of experimentally induced cardiac infarction in the dog. Favorable clinical results are reported not only when theophylline is used in the treatment of acute coronary occlusion but also in instances of paroxysmal dyspnea and in cases of angina pectoris. The beneficial influence probably results from its action in promoting the extent of the collateral coronary circulation. The importance of long continued treatment is emphasized.

#### HEART FAILURE AND ITS TREATMENT

Harrison<sup>68</sup> has published a book of three hundred and forty-nine pages, entitled "Failure of the Circulation," which deals with studies carried out by himself and his colleagues on circulatory disorders as observed in patients with diseases of the heart and in experimental animals. The problem is approached from a clinicophysiology aspect and, quite naturally, stresses the point of view of the author. In the final chapter his chief conclusions are summarized as follows:

Aside from the coronary syndrome which is initially a local circulatory disturbance, general functional impairments of the cardiovascular system are of three main types, which may occur singly or in various combinations:

I. Acute circulatory failure (the hypokinetic syndrome) includes the conditions which have usually been classified as "collapse," "primary shock" and "secondary shock." It may be of cardiac origin but is usually due to disturbances in the periphery. Its chief subjective manifestation is weakness and the most important

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67 Fowler, W. M., Hurevitz, H. M., and Smith, Fred M. Effect of Theophylline Ethylenediamine on Experimentally Induced Cardiac Infarction in the Dog, *Arch Int Med* **56** 1242 (Dec.) 1935. Smith, Fred M., Rathe, Herbert W., and Paul, W. D. Theophylline in the Treatment of Disease of the Coronary Arteries, *ibid* **56** 1250 (Dec.) 1935.

68 Harrison, Tinsley Randolph. *Failure of the Circulation*, Baltimore, Williams & Wilkins Company, 1935.

objective signs are feeble pulse, tachycardia, decrease in the arterial blood pressure, and decline in the pulse pressure. Less constantly the heart sounds are diminished in intensity and approach each other in quality. These phenomena are dependent on or related to diminution of the cardiac output, which may be brought about in several different ways.

1 The hematogenic type of the hypokinetic syndrome, which has been called "secondary shock," is due to decrease in the circulating blood volume, such as occurs in hemorrhage, traumatic shock or following excessive dehydration from any cause.

2 The neurogenic type of the hypokinetic syndrome ("primary shock") is due to vascular dilatation dependent on disturbances in the nervous system, such as fainting, spinal anesthesia and injuries to the brain or spinal cord.

3 The vasogenic type of the hypokinetic syndrome is also brought about by dilatation of the arterioles, but is dependent on influences which act directly on the vessels, such as histamine and nitrites.

4 The cardiogenic type of the hypokinetic syndrome is usually produced by sudden severe damage to the heart, such as occurs in coronary thrombosis, or by prolonged beating as in persistent paroxysmal tachycardia. Less commonly this symptom-complex may be brought about by sudden and marked slowing of the heart, or by inadequate cardiac filling as the result of pericardial thickening. In such instances the manifestations of congestive heart failure and those of acute circulatory collapse may coexist.

II The overactive heart (the hyperkinetic syndrome), like the hypokinetic disturbances, is usually of peripheral rather than of cardiac origin. Its chief subjective manifestation is palpitation and its objective phenomena are forcible diffuse cardiac impulse, loud heart sounds, apical and especially basal systolic murmurs, moderate tachycardia, increased arterial pulsations, bounding or even collapsing pulse, and increased pulse pressure. Its most common causes are hyperthyroidism, severe anemia, fever, and certain types of cardiac neurosis. Some of the last patients exhibit these phenomena only on mild exertion and to these the terms "neurocirculatory asthenia" (which is a misnomer), "soldier's heart" and "effort syndrome" have been applied. The phenomena of the hyperkinetic disturbance are similar to those which occur in normal persons during physical exertion and are due mainly to the same underlying physiological mechanism—increase in the cardiac output.

III Congestive heart failure (the dyskinetic syndrome) designates the clinical picture usually called "cardiac decompensation." The primary disease process may involve either the heart—as in valvular diseases, or the peripheral vascular apparatus—as in hypertension, but in each instance the final result is to render the heart inefficient in the performance of its work. The main subjective manifestation of this syndrome is dyspnea, and the most important objective phenomena are cardiac enlargement, decrease in vital capacity, râles at the lung bases, distension of the systemic veins, enlargement of the liver, edema, and the accumulation of fluid in the body cavities.

This clinical picture has been believed by many to be dependent on inadequate blood supply to the tissues and it is true that accurate measurements of the cardiac output reveal low values in the majority of patients with congestive heart failure. However the thesis that dyspnea, edema, and the other important manifestations of congestive failure are dependent on diminished flow through the tissues is untenable for several reasons, of which the following are the most important.

(a) Edema and dyspnea are not usually present in patients with disorders, such as hemorrhage or traumatic shock, which are known to be associated with marked decrease in the cardiac output, and are not produced in experimental animals by diminution of the cardiac output

(b) Some patients with congestive heart failure have values for the cardiac output which are well within the normal range. Disappearance of congestive heart failure is not associated with constant increase in the cardiac output even in patients who exhibit diminution of this function

(c) Those therapeutic measures, such as venesection, and the use of digitalis and of diuretic drugs, which cause clinical improvement in persons with congestive heart failure, do not regularly cause an increase in the output of the heart

This evidence seems to indicate conclusively that the "forward failure" (diminished output) theory is erroneous. On the other hand the alternate theory of "backward failure" ("back pressure") appears to fit the facts

According to this hypothesis the essential factor in the production of the clinical manifestations of heart failure is accumulation of blood in those vascular areas which drain toward the failing chamber of the heart. Thus failure, *i e*, dilatation, of the left ventricle leads to a rise in the pressure in the left auricle which causes engorgement of the lungs. Such an increase in the intrathoracic blood volume has been demonstrated not only by the findings at necropsy but also by measurements—made by indirect methods—during life. Since the amount of blood flowing through the lungs, *i e*, the cardiac output, is not augmented the increase in the size of the pulmonary vascular bed must be associated with a diminution in the velocity of the blood flow, and this likewise has been demonstrated. Similar changes occur in the systemic circuit when the right ventricle fails. In most patients the underlying cause of cardiac disease is of such a nature as to impose the primary strain on the left side of the heart. If the "back pressure" theory is correct congestive phenomena should develop first in the lungs and later in the systemic circulation. This is exactly what occurs, as is shown by the fact that diminution in the vital capacity precedes an increase in the systemic venous pressure in almost all cases.

According to this (the "back pressure") theory the manifestations of cardiac failure are to be ascribed chiefly to a rise in pressure in the veins draining into the failing side of the heart. That cardiac edema is due to such a rise in systemic venous pressure is probably generally admitted. Concerning dyspnea no such agreement exists, many persons still ascribing it to diminished cerebral blood flow—an hypothesis which is, in the main, erroneous.

Investigations of cardiac dyspnea have shown that it occurs under conditions which cause labored breathing. The excessive respiratory effort and the subjective distress are not cause and effect but are parallel responses. Dyspnea, the subjective phenomenon, represents the effect on the cerebral cortex of the same factors which, when acting on the medulla, produce the labored breathing. The important point is that one can measure the respiratory effort and thereby can achieve a quantitative expression of its subjective concomitant, dyspnea. When there is no obstruction to respiration the breathing is labored in proportion to the closeness with which the actual ventilation approaches the maximum possible ventilation. The actual ventilation can be readily determined and the maximum possible ventilation depends on the vital capacity, which can also be easily measured. Simultaneous observation of these two functions allows a quantitative formulation of the degree of dyspnea.

The respiratory reserve can be encroached on and the breathing made to become labored by any process which either decreases the vital capacity or which increases

the ventilation. In patients with congestive heart failure the vital capacity is decreased as a result of congestion of the lungs. This predisposes the subject to dyspnea, but dyspnea may be absent as long as the breathing is not stimulated. The several types of cardiac dyspnea are to be attributed to various agents which cause respiratory stimulation in a patient with diminished respiratory reserve (decreased vital capacity). The study of the mechanism of cardiac dyspnea therefore resolves itself into an investigation of these agents.

It was formerly believed that dyspnea in cardiac disease could be attributed to chemical changes in the arterial blood as a result of inadequate pulmonary ventilation. Such alterations are encountered in moribund patients and in those who have severe pulmonary edema or advanced emphysema but are absent in the majority of patients with congestive failure. The concept that cardiac dyspnea is dependent on inadequate supply of blood to the respiratory center as a result of subnormal cardiac output has been shown to be erroneous by the observation that the composition of the blood in the internal jugular vein is not usually altered by procedures, such as mild exercise and the assumption of the recumbent posture, which cause dyspnea.

In general, the stimulation of breathing in persons with cardiac disease is of reflex rather than of chemical origin. Of the several reflexes concerned the most important one arises in the lungs, and is due to the effect of congestion on the afferent vagal endings. This reflex is mainly responsible for orthopnea and for cardiac asthma, and it is a factor in the production of dyspnea on exertion. Dyspnea on exertion, however, is more closely related to reflex respiratory stimulation from the moving muscles and from the action of an increased venous pressure, brought about by exertion, on the afferent vagal terminals in the venous end of the heart.

Dyspnea is then, in the main, to be ascribed to pulmonary congestion as a result of "back pressure" from the left side of the heart. The increase in pulmonary pressure eventually leads to failure of the right ventricle and edema. Dyspnea usually precedes edema because the underlying disease process ordinarily imposes the initial strain on the left side of the heart.

Unlike dyspnea and edema, enlargement of the heart, which is the other cardinal manifestation of cardiac disease, is not a result of heart failure, but is brought about by the same underlying disorder which produces heart failure.

Cardiac enlargement consists of two processes. One of them is hypertrophy which is dependent on overwork, either of the heart as a whole or of portions of it, as a result of disease of other parts. The thickening of the muscle fiber tends at first to make it more powerful. After a time this mechanical advantage is more than offset by a chemical disadvantage, for the recovery process in the heart muscle, being dependent on the diffusion of oxygen into it, becomes hampered by the thicker fiber. This is especially important when the heart rate is rapid, for in this condition the duration of diastole (the period in which recovery must take place) is diminished. Hence, even if the burden on the heart is not increasing, the hypertrophied heart tends to become fatigued. Fatigue leads to dilatation, which has the double advantage of diminishing the thickness and of increasing the surface of the fibers. Dilatation is the immediate response of the heart to increase in work and hence probably precedes hypertrophy as well as succeeding it. But dilatation—this second type of cardiac enlargement—has its disadvantages also. The dilated heart, in order to perform a given amount of work, requires more oxygen than does the undilated heart. If, because of the thickened fiber, coronary disease, or other factors, the needed oxygen is not available the heart will dilate still more and will require still more oxygen to perform its previous work. And so the cycle proceeds.



For these reasons the enlarged heart tends to become fatigued. Cardiac fatigue is a phenomenon of fundamental importance in relation to cardiac failure. When studied under conditions—such as exist in the heart-lung preparation—in which the various circulatory factors can be controlled and the action of the heart readily observed, it is found to take place in three stages which merge into each other gradually.

(a) The heart dilates, all other factors including the output remaining constant. This stage probably corresponds to the clinical condition of a patient who has no congestive phenomena but who has a limitation of effort, for the reserve power of a heart consists of its ability to dilate, and a heart which is already dilated has begun to encroach on its reserve.

(b) The output begins to diminish somewhat but returns to its previous level if the venous pressure is sufficiently raised. At the same time the degree of dilatation increases somewhat. This stage appears to correspond to the clinical state of a patient with a normal or nearly normal cardiac output but with a considerably dilated heart, and with increased venous pressure and consequent phenomena of congestive failure.

(c) The output diminishes rapidly and in a short time the heart ceases to beat. This is a terminal state and corresponds to the moribund patient with hypokinetic as well as dyskinetic phenomena.

The analogy with the experimentally fatigued heart allows us to define heart failure. It may be said to begin when, in order to perform a given amount of work, the diastolic volume of the heart increases. Expressed otherwise, it may be said that the reserve power of the heart is beginning to fail when the size of that heart is increased in proportion to its output. Similarly, congestive heart failure may be defined as a state in which venous pressure is increased disproportionately to the cardiac output, or as the condition in which the heart can maintain a given output only when driven to do so by a greater filling pressure.

My conclusion, then, is that the clinical manifestations of congestive heart failure are due to "back pressure," dyspnea being brought about by congestion of the lungs which is a result of "back pressure" from the left side of the heart, and edema being due to congestion of the systemic circulation dependent on "back pressure" from the right side of the heart. In both instances the rise in pressure in the veins is dependent on dilatation of the chambers of the corresponding side of the heart, the dilatation in its turn being a manifestation of fatigue of the cardiac muscle. The dilated heart is an inefficient pump for, although it may supply an adequate amount of blood to the tissues, it expends excess energy in order to carry on this work. Heart failure is to be attributed, in the main, to inefficiency rather than to insufficiency of the myocardium.

Vaquez<sup>69</sup> expressed the belief that there is a marked revival of interest in the study of digitalis, due chiefly to the widespread dissatisfaction with present galenic preparations which have enjoyed great preference because the total drug base is more useful than any one of its components and because of the practical ease of administration. He remarked that the variability in therapeutic activity and the instability of galenic preparations which have apparently caused so much

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<sup>69</sup> Vaquez, H. Preparations galeniques et glucosides de la digitale, *Arch d mal du cœur* 28 185, 1935.

dissatisfaction in many places have not especially troubled clinicians in America. He told how the Hygiene Section of the League of Nations took up the study of standardization of galenic preparations but after five years' study concluded that it was still too early to make a decision as to the choice of a method of extraction of the drug or a method of standardization and that consequently an international unit cannot be fixed. Ingenious researches are described which were performed with the intention of isolating all the glucosides of digitalis, studying their several qualities and synthetically regrouping them so as to reconstruct the global activity of the drug. Up to the present these attempts have not met with great success.

Fraenkel<sup>70</sup> stated that it is possible to insure the same degree of accuracy in administering digitalis to patients as is demanded in a pharmacologic experiment on the lower animals, but in order to do this it is necessary to dispense with the galenic preparations and their many substitutes and, in addition, to change the usual routine of administration. When one considers the large variation in different galenic preparations, the decreased effect resulting from their reactions with the acid gastric juice and intestinal alkalis when they are given by mouth, the faulty absorption due to the surface activity and adsorption of the drug, and the incalculable loss under the pathologic conditions of circulatory failure, it must be concluded that the only suitable method of quantitative administration is intravenous injection.

In his choice of a drug Fraenkel was guided by the results of experiments on cats in which different glucosides of digitalis were compared, as to the degree and duration of their action. Strophanthin Kombé was chosen because its action could be maintained by repeated injections without the appearance of toxic effects attributable to cumulative action of the drug. Tens of thousands of injections of this drug have been given to patients without there resulting any of the dreaded complications.

He cited a series of cases in which strophanthin was used only after the oral administration of digitalis had proved unsuccessful. Excellent therapeutic results were usually obtained. It was necessary to adhere to exact dosage and to note the effect of each dose. Patients who needed little strophanthin and displayed marked diuresis had, usually, a better prognosis than those who required larger doses yet lost edema fluid more slowly. Fraenkel stated

it is by no means exclusively cases of heart failure with auricular fibrillation or frequent and regular pulse which respond to strophanthin administration

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<sup>70</sup> Fraenkel, A. Pharmacological Aspect of Digitalis Therapy, *Lancet* 2 1101, 1935

Complete success is met with even when the pulse is infrequent and regular. In these cases the muscular effect of strophanthin is more prominent than the vagal.

This attempt, however, to evaluate a rational digitalis therapy from a knowledge of experimental pharmacology, and to describe the peculiar importance of the intravenous route in connection with the glucoside which is most suitable for this mode of administration, is not to be regarded as a revolt from the customary empirical use of preparations of digitalis by mouth. Withering's therapy retains its position in the treatment of heart failure when such is not of too severe a degree or of not too long a standing.

Bedford and Campbell<sup>71</sup> have carried out clinical tests with strophanthin emini, which yields on analysis a complex mixture of glucosides similar in type to that obtained from strophanthin kombé. Strophanthin emini is best given intravenously and provokes a digitalis-like action on the heart in from fifteen to thirty minutes. It appears to act more quickly than digoxin,<sup>72</sup> which has recently been isolated and tested clinically. It has no advantage over digitalis and has one great disadvantage, in that the therapeutic and the toxic dose are so close together.

The recently isolated cardiac glucoside thevetin<sup>73</sup> has been subjected to further clinical trial. In clinical use it is best given intravenously. It has a digitalis-like action, with a potency about one-seventh that of ouabain. It appears to be more toxic than digitalis when comparable doses are given.

Carr and Mayer<sup>74</sup> have studied the effect of scillonin, a derivative of squill, on 104 patients with cardiac decompensation. This drug has the same therapeutic and toxic effects as digitalis. Because nausea appears as a late rather than as an early toxic effect of scillonin, that drug is of advantage for certain patients who take digitalis with difficulty because of gastric distress early in the course of medication. More care is required in the administration of scillonin, however, than in the use of digitalis.

Good clinical results have followed the use of diuretic drugs, either continuously or in long courses, in the early stages of heart failure. It is unfortunate that these drugs are not more commonly used before the advent of frank cardiac edema. This view has been reemphasized

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71 Bedford, D. E., Campbell, M., and Wood, P. H. The Treatment of Auricular Fibrillation with Strophanthin Emini, *Guy's Hosp Rep* **85** 185, 1935.

72 Wayne, E. J. Clinical Observations on Two Pure Glucosides of Digitalis, Digoxin, and Digitalinum Verum, *Clin Sc* **1** 63, 1933.

73 Arnold, Harry L., Middleton, William S., and Chen, K. K. The Action of Thevetin, a Cardiac Glucoside, and Its Clinical Application, *Am J M Sc* **189** 193, 1935.

74 Carr, James G., and Mayer, Jacob D. Clinical Experience with a Derivative of Squill, *Arch Int Med* **56** 700 (Oct) 1935.

by Friedman and his co-workers,<sup>75</sup> who have frequently noticed the amelioration of cardiac symptoms after the administration of diuretics to patients with little or no demonstrable edema. Improvement occurred even when the diuresis was of slight degree. Objective measurements of the effect of diuretics on circulatory and respiratory functions were made on a group of hospitalized patients who complained chiefly of dyspnea but who had minimal pitting or latent edema. Clinical improvement was sometimes associated with an increase in vital capacity, but often this increase was so slight as to be of questionable significance. Decrease in spinal fluid pressure and in blood volume may have played a rôle, but these factors were not studied. Consistent changes in heart rate, oxygen consumption and cardiac output did not occur. Two possible factors probably influenced cardiac output following the administration of diuretic drugs. One was the decrease in flow of blood through the edematous tissues, which tended to decrease the cardiac output, and the other was the reduction of myocardial edema, which may have led to an increase in the cardiac output.

The changes in the alkali reserve and in the protein content of the blood following the use of diuretics have been investigated.<sup>76</sup> The results obtained by various workers are not in agreement regarding the mechanism whereby values for plasma protein rise after diuresis following the administration of salyrgan.

It is still too early to evaluate correctly the procedure of total thyroidectomy in the treatment of heart failure.<sup>77</sup> Three years' experi-

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75 Friedman, Ben, Resnik, Harry, Calhoun, J. A., and Harrison, T. R. Effect of Diuretics on the Cardiac Output of Patients with Congestive Heart Failure, *Arch Int Med* **56** 341 (Aug.) 1935.

76 Bryan, A. Hughes, Evans, William A., Jr., Fulton, Marshall N., and Stead, E. A., Jr. Diuresis Following the Administration of Salyrgan. Its Effect on the Specific Gravity, the Total Nitrogen and the Colloid Osmotic Pressure of the Plasma of Normal and Edematous Dogs, *Arch Int Med* **55** 735 (May) 1935. Schally, A. O. Veränderungen der Bluteiweisskörper bei der Salyrgan-diurese, *Deutsches Arch f klin Med* **177** 368, 1935. Gottsegen, G. Einfluss der Diuretika auf die Alkalireserve des Blutes, *Wien klin Wchnschr* **48** 1116, 1935.

77 Berlin, David D. Total Thyroidectomy for Intractable Heart Disease. Summary of Two and One-Half Years' Surgical Experience, *J A M A* **105** 1104 (Oct 5) 1935. Blumgart, H. L., Berlin, D. D., Davis, D., Riseman, J. E. F., and Weinstein, A. A. Total Ablation of Thyroid in Angina Pectoris and Congestive Failure. XI. Summary of Results in Treating Seventy-Five Patients During the Last Eighteen Months, *ibid* **104** 17 (Jan 5) 1935. Blumgart, H. L., Riseman, J. E. F., Davis, D., and Weinstein, A. A. Treatment of Angina Pectoris and Congestive Failure by Total Ablation of the Normal Thyroid. XIV. Results in Arteriosclerotic Heart Disease, *Am Heart J* **10** 596, 1935. Clark, Richard J., Means, James H., and Sprague, Howard B. Total Thyroidectomy

ence indicates that this operation is of significant value when limited to a few carefully selected cases. Its greatest value, by far, is in the treatment of angina pectoris, but even in cases of that disorder there is no cause for great enthusiasm, and certain conditions must be fulfilled before thyroidectomy is suggested (not urged). The probable life expectancy of the patient without operation must be at least from one to two years. In patients with angina pectoris the presence of complicating disease of significant degree, especially of involvement of the heart, lungs, kidneys or liver, has to be ruled out. It must be shown that available medical treatment, including rest in bed for one month, is inadequate. Furthermore, the preoperative basal metabolic rate must not be lower than —15 per cent. Technically the operation does not involve undue risk when skilfully performed. If these criteria are given full consideration, one may with confidence predict genuine improvement in regard to anginal attacks in about three fourths of the cases.

Available studies indicate a wide divergence of opinion regarding the value of thyroidectomy in patients with congestive heart failure, a few patients are undoubtedly suitable for this procedure. It is impossible here to discuss adequately the difficult problem of selection of cases. Reference may be made to the aforementioned reports

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for Heart Disease. Experiences with Twenty-One Patients at the Massachusetts General Hospital, *New England J Med* **214** 277, 1935. Levine, S. A., and Eppinger, E. C. Further Experiences with Total Thyroidectomy in the Treatment of Intractable Heart Disease, *Am Heart J* **10** 736, 1935. Riseman, J. E. F., Gilligan, D. R., and Blumgart, H. L. Treatment of Congestive Heart Failure and Angina Pectoris by Total Ablation of the Normal Thyroid Gland. XVI. The Sensitivity of Man to Epinephrine Injected Intravenously Before and After Total Thyroidectomy, *Arch Int Med* **56** 38 (July) 1935.

## Book Reviews

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**Arthritis and Rheumatoid Conditions Their Nature and Treatment** By Ralph Pemberton Price, \$5 50 Pp 455, with 69 engravings and a colored plate Philadelphia Lea & Febiger, 1935

The long-overdue second edition of this work, the first edition of which was published in 1929, will be warmly received. First written to help place the subject of arthritis on a plane which would arouse the interest and attention then lacking, the work now attempts to incorporate data which have accumulated in the past six years. Consequently the volume has been expanded one hundred pages, and many illustrations have been added.

The book maintains its same general order, starting with a brief historical approach, leading to arthritis as an economic problem and then to its pathology, dynamic pathology, symptomatology and treatment and to related conditions. One is impressed by the statistics quoted showing the magnitude of arthritis as a social problem. Surveys show that cases of this condition constitute 9 per cent of all cases of disease, outstripping those of tuberculosis and organic heart disease and out-ranked only by cases of accidents. In general, Pemberton follows the classification of Nichols and Richardson and that of Knaggs in classifying arthritis into atrophic and hypertrophic types. However, he believes that these types have many features in common and discusses the etiology and treatment with regard to the syndrome of the disease as a whole. Under "Dynamic Pathology" are discussed the influences of basal metabolism and of protein, lipid, carbohydrate, salt and water metabolism, as well as the acid-base balance, circulatory, respiratory, cutaneous and renal function and the blood picture. Many of the discussions are unduly long in relationship to their importance, as is the space allotted to a review of the author's experiments which gave negative results. Changes in the circulation and in the carbohydrate metabolism are of especial interest.

Approximately 175 of the 455 pages are devoted specifically to treatment. All the important aspects are discussed—focal infection, the rôle of the intestine, diet, colonic irrigation, vaccines, physical therapy, drugs and medicinal measures. All are evaluated principally in the light of the author's own extensive experience. He seeks to recommend no one factor of therapy alone but to emphasize that the factors known to have a favorable influence should be coordinated into a whole, with necessary individualization.

The second edition insures this volume a continued important place in medical literature.

**Thérapeutique de l'ulcère gastro-duodénal** By Jean Gatellier and François Moutier Price, 22 francs Pp 236 Paris Gaston Doin & Cie, 1935

In this monograph Gatellier and Moutier present to the medical profession their experiences with the therapeutics for gastroduodenal ulcer. The material is derived from 1,200 personally treated patients. There is no bibliography or review of the literature on the subject. The authors merely report their experiences and occasionally refer to the work of physicians prominent in this field.

Practically the entire discussion is devoted to treatment. The first few pages contain a dissertation on the anatomic, clinical and pathologic aspects of the disease. Throughout the monograph brief discussions of the clinical manifestations of the various phases and complications of the condition, such as hemorrhage, perforation, obstruction and the like, that are being treated by one method or another, are given. They include a discussion of the findings in roentgenologic, gastroscopic and other special examinations, when these were used in the study of the cases.

The therapeutic presentation includes a consideration of the medical and surgical treatment of uncomplicated and complicated forms. The authors discuss pre-operative and postoperative treatment, emphasizing joint medical and surgical treatment in these cases. They present a list of diets, prescriptions for patients and formulas for large quantity preparations of mixtures of drugs which they employed in the treating of their patients. The indications and rationale for their various therapeutic methods of choice under diverse conditions are also briefly presented.

From the monograph one realizes that the authors do not present any definitely superior method for the treatment of gastroduodenal ulcer and that they experienced results and difficulties with their methods similar to those obtained by different methods employed by other physicians. Nothing revolutionary is presented, but one who is interested in the therapy employed by the authors in treating their large series of patients can adequately learn it from this intelligible presentation.

**Clinical Laboratory Methods and Diagnosis** By R. B. H. Gradwohl, M.D., director of the Gradwohl Laboratories, St. Louis. Price, \$8.50. Pp. 1028, with 328 illustrations and 24 color plates. St. Louis: C. V. Mosby Company, 1935.

Gradwohl in his preface states that this book was written to help the clinician, the laboratory worker and the medical student to learn laboratory diagnosis. It is divided into seventeen chapters more or less according to the traditional fashion for a textbook of this nature. The division of the space allotted to different subjects is of some interest, as it reflects so well current medical enthusiasms, 64 pages are devoted to urinalysis, 81 to blood chemistry, 181 to hematology and 155 to clinical bacteriology. The standard picture of the accepted procedures in the different fields is given in great detail. A carefully written chapter is devoted to the subject of postmortem examinations, telling how to obtain permission to make such examinations, and, permission having been granted, how to perform them most perfectly.

On the whole, the volume is a happy venture. As is stated in the review which appeared in *The Journal of the American Medical Association* (104:2291 [April 22] 1935), the book is an unusually complete work on clinical laboratory methods and their interpretation and is a fertile source of information.

**The Treatment of Diabetes Mellitus** By Elliott P. Joslin, M.D., with the cooperation of Howard F. Root, M.D., Priscilla White, M.D., and Alexander Marble, M.D. Fifth edition. Price, \$6. Pp. 620, with 144 tables and 7 illustrations. Philadelphia: Lea & Febiger, 1935.

In his preface to the new edition Joslin states "Diabetes is a disease for young doctors," and acting in this spirit one finds that Root, White, Marble and others are now associated with him in writing certain sections. The senior author shows, however, no signs of age or decay and deals with the subject with all his former vigor and clarity. Since the previous (1928) edition the book has been shortened by about four hundred pages, but in spite of this the reviewer fails to discover any phase or, indeed, any detail of diabetes which is not adequately discussed. "Joslin" definitely remains the standard guide for American practice, a sound, well tempered point of view is maintained, going neither to one extreme nor the other on the matter of carbohydrate ration, each point is buttressed against the solid background of the author's vast clinical experience as well as statistics from the literature. The chapters on the complications of diabetes, diabetic surgery, diabetes in childhood and pregnancy in diabetes contain valuable material not readily accessible elsewhere in textbooks.

**Human Pathology** By Howard T Karsner, Professor of Pathology, Western Reserve University With an introduction by Simon Flexner Fourth edition, revised Price, \$10 Pp 1013, with 18 colored and 443 plain illustrations Philadelphia J B Lippincott Company, 1935

Karsner's "Human Pathology" has been accepted widely as a text by teachers, students and practitioners of medicine The fourth edition, now offered, has been revised and extended to include some of the more recent advances in pathology Certain chapters have been rewritten completely The general plan of arrangement is essentially the same as in the preceding editions The twelve chapters of the first part concern general pathology, the ten of the second part are special The preceding editions have been used largely by undergraduate students of medicine and has been an excellent text for them The fourth edition will serve the same general group and is recommended to instructors of general and special pathology in medical schools for the guidance of their students

**Diseases of the Liver, Gall Bladder, Ducts and Pancreas** By Samuel Weiss Price, \$10 Pp 1099, with 358 illustrations and 6 plates New York Paul B Hoeber, Inc, 1935

This monumental compendium cannot be reviewed in detail in the space available Gotten up in the beautiful Hoeber format, with a wealth of excellent illustrations and an extensive bibliography and index, it contains an encyclopedic account of practically everything pertaining to the liver, gallbladder and pancreas To the reviewer the value of the book lies not so much in the discussions of common topics which are adequately dealt with in ordinary textbooks as in the collection of all sorts of rare disorders and anomalies information about which is usually obtainable only in the periodic literature This encyclopedic form of treatment sometimes disturbs the perspective a little and makes it hard to separate what is of established value from material which is less useful, but this can hardly be avoided in a reference book of this sort The price is reasonable It is perhaps to be regretted that the work was not divided into two volumes, as the book is heavy and difficult to handle

**Abnormal Arterial Tension** By Edward J Stieglitz, M D, Assistant Clinical Professor of Medicine, Rush Medical College Price, \$3 Pp 261, with 66 illustrations New York National Medical Book Company, Inc, 1935

This book is one of a series of the National Medical Monographs edited by Dr Morris Fishbein The other subjects so far discussed in the series are obstetrics, industrial medicine, colitis and diseases of the skin and chest One gathers that the National Medical Monographs are not unlike similar medical monographic systems that have appeared recently in France and are designed especially to be of use to physicians in this country

This particular book by Dr Stieglitz is nice-looking It slips easily into one's pocket, so that it can be read at odd moments It is well printed It is simply written in clear, concise English The illustrations and diagrams are excellent The various aspects of normal arterial tension and what is known about the cause and treatment of hypertension and hypotension are intelligently discussed in the light of present knowledge On the whole, the book should prove a useful member of its group

**Experimental Pneumothorax** By Kjeld Tørning Paper Pp 161, with 31 figures and 79 protocols Copenhagen Nyt Nordisk Forlag, 1933

This dissertation reviews the history of therapeutic pneumothorax and the theories of its *modus operandi* and gives the results of Tørning's experiments on animals Of the usual laboratory animals, the rabbit is the only one that has a sufficiently rigid mediastinum to be useful in the study of unilateral collapse A



new technic was used to study the rates of ventilation of the two lungs separately without opening the pleural cavity or injuring the thoracic skeleton. The changes in the ventilation of the two sides are described in detail for open, and for various degrees of closed, unilateral pneumothorax. Measurements of the rate of oxygen consumption and the degree of oxygenation of the arterial blood were used to calculate the rate of circulation through the lungs and enabled Tørning to show that in a collapsed lung the circulation is so reduced that it may sink to less than 15 per cent of the total pulmonary circulation.

**Living Along with Heart Disease** By Louis Levin, M D, cardiologist to the St Francis Hospital and New Jersey State Prison Hospital, Trenton, N J. Price, \$1.50. Pp 126. New York: The Macmillan Company, 1935.

This is a manual for patients with heart disease, not unlike the manuals on diabetes or similar works already available for the inquisitive layman. It is intelligently written and discusses heart disease fairly and honestly, enlivened from time to time by apt anecdotes of cases in places that otherwise might seem gloomy or depressing. Levin states that the purpose of the book is to present to the reader a simplified explanation of various aspects of heart disease with the ultimate hope of instilling sane optimism in the patient's philosophy regarding this disorder. He has accomplished a step in the right direction.

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## News and Comment

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### AMERICAN HEART ASSOCIATION, INC

The Twelfth Scientific Session of the American Heart Association will be held on Tuesday, May 12, 1936, from 9:30 to 5:30 p. m., at Hotel Phillips, Kansas City, Mo. The program will be devoted to cardiac insufficiency.

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### CORRECTION

In the article by Dr. M. M. Wintrobe in the February issue (*ARCH. INT. MED.* 57:289, 1936), on page 293, line 10, "inversely proportional to the degree of anemia" should read "inversely proportional to the number of red cells."

## CLINICAL OBSERVATIONS ON NONTROPICAL SPRUE

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By most North American physicians sprue has always been considered as a specific tropical disease, endemic and rarely, if ever, encountered among natives of temperate climates. It was described first by Hillary,<sup>1</sup> from the Barbadoes, in 1766, and the subsequent writings of many authors have served to establish the habitat of the disease in the tropics. The idea that sprue, or a condition closely resembling it, might occur in nontropical climates is of rather recent origin. From a historical standpoint it is interesting to note that Vincent Ketelaer published an account of a disease resembling sprue, under the title "De aphthis nostratibus, seu Belgarum Sprouw," in 1699, which antedated the description by Hillary. As may be inferred from the title, the cases described were apparently instances of an endemic disease and were encountered in Belgium. Gee<sup>2</sup> (1888) was the first modern commentator on spruelike diseases in nontropical environments. He described the condition as the "coeliac affection" and noted that it afflicted adults who had never left England. Herter<sup>3</sup> rediscovered Gee's disease in 1908 and made the first metabolic studies of it. One year later Huebner<sup>4</sup> made a somewhat similar report in Germany. During the present century an increasing number of reports of sprue-like diseases occurring in nontropical climates have appeared in the literature. Wood<sup>5</sup> (1915) was one of the first to call attention to

From the Division of Medicine, The Mayo Clinic

Read in the Section on Gastro-Enterology at the Twenty-Eighth Annual Meeting of the Southern Medical Association, San Antonio, Tex., Nov 15, 1934

1 Hillary, cited by Major, R. H. *Classic Descriptions of Disease, with Biographical Sketches of the Authors*, Springfield, Ill., Charles C. Thomas, Publisher, 1932

2 Gee, Samuel. On the Coeliac Affection, *St. Barth. Hosp. Rep.* **24**: 17, 1888

3 Herter, C. A. On Infantilism from Chronic Intestinal Infection, Characterized by the Overgrowth and Persistence of Flora of the Nursing Period, New York, The Macmillan Company, 1908

4 Huebner, O. Ueber schwere Verdauungsinsuffizienz beim Kinde jenseits des Sauglingsalters, *Jahrb. f. Kinderh.* **70**: 667, 1910

5 Wood, E. J. The Occurrence of Sprue in the United States, *Am. J. M. Sc.* **150**: 692 (Nov.) 1915

the reports of the disease in the United States. He cited a number of reports from the American literature, including that of Simon<sup>6</sup> of New Orleans. Since then numerous accounts of nontropical sprue have appeared, both from this country and from Northern Europe, and several writers, notably Simon,<sup>7</sup> have commented on the frequency with which the disease is encountered in the southern part of the United States. Thaysen<sup>8</sup> (1932) mentioned thirty-four cases, including a number that had not been noted previously. Mackie<sup>9</sup> (1933) collected reports of seventy-one cases from the literature and added a report of a carefully studied case of his own. His review included reports of several cases which previously had been collected by Thaysen and others which admittedly were of doubtful authenticity. Bennett, Hunter and Vaughan<sup>10</sup> (1932) made an exhaustive report on a series of fifteen cases which they had studied personally and collected reports of a number of additional cases from the literature. Numerous additional cases have been cited from the literature in previous reports from the Mayo Clinic.<sup>11</sup> It would appear from the references which have been mentioned and from more recent reports<sup>12</sup> that a disease resembling sprue is being

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6 Simon, S. K. Report of a Probable Case of Sprue, *South M J* **4** 466 (July) 1911

7 Simon, S. K. Some Observations on Sprue and Its Prevalence in the South, *South M J* **14** 255 (April) 1921

8 Thaysen, T. E. H. Nontropical Sprue. A Study in Idiopathic Steatorrhea, Copenhagen, Levin & Munksgaard, 1932

9 Mackie, T. T. Nontropical Sprue, *M Clin North America* **17** 165 (July) 1933

10 Bennett, T. I., Hunter, D., and Vaughan, J. M. Idiopathic Steatorrhea (Gee's Disease). A Nutritional Disturbance Associated with Tetany, Osteomalacia, and Anemia, *Quart J Med* **1** 603 (Oct) 1932

11 (a) Snell, A. M., and Camp, J. D. Roentgenologic Findings in Chronic Idiopathic Steatorrhea, *Arch Int Med* **53** 615 (April) 1934. (b) Constan, C. R., and Partch, W. T. An Unusual Case of Nutritional Disturbance Showing Symptoms of Pellagra, Osteomalacia and Tetany, *Minnesota Med* **12** 40 (Jan) 1929. (c) Curry, F. S. Chronic Steatorrhea with Tetany. Report of a Case, *Proc Staff Meet, Mayo Clin* **7** 501 (Aug 31) 1932. (d) Snell, A. M. Chronic Steatorrhea with Tetany. Report of Two Cases, *M Clin North America* **15** 1593 (May) 1932. (e) Snell, A. M., and Camp, J. D. Chronic Idiopathic Steatorrhea. Roentgenologic Observations. *Arch Int Med* **53** 615 (April) 1934. (f) Snell, A. M., and Haben, H. C. Tetany and Chronic Diarrhea, *Ann Int Med* **1** 694 (March) 1928

12 (a) Anderson, A. G., and Lvall, Alexander. Two Cases of "Fatty Diarrhoea," with Special Reference to Nitrogen Metabolism, *Quart J Med* **2** 339 (July) 1933. (b) Bowne-Davies, A. A Case of Steatorrhea with Stomatitis, Leucopenia and Anaemia, *Guy's Hosp Rep* **84** 57 (Jan) 1934. (c) Lister, W. A. Idiopathic Steatorrhea of Adults. A Record of Two Cases, *Lancet* **2** 15 (July 1) 1933. (d) Roberts, C. G. Coeliac Disease in an Adult Treated with Sugarless Milk, Bananas and Meat, *Lancet* **1** 130 (Jan 20) 1934. (e) Thaysen, T. E. H. "Coeliac Affection", Idiopathic Steatorrhea, *Lancet* **1** 1086 (May 25) 1929

recognized with increasing frequency in nontropical climates, it is probable that considerably more than a hundred cases are now on record. There has been no uniformity in the nomenclature used in describing the disease, and it has been described variously as nontropical sprue, idiopathic steatorrhea, adult celiac disease, intestinal lipodystrophy, Gee-Herter's disease and so forth.

I have had an opportunity to observe ten cases personally at the Mayo Clinic since 1927, these constitute the basis for this report. During this period a number of other cases of similar conditions have been observed at the clinic, these are not included either because of the lack of essential diagnostic data or because of an insufficient period of observation. The ten cases are reported not only to call attention to the frequency with which spruelike disease is being encountered in nontropical climates but also because of the relation of this condition to the deficiency diseases and particularly because of the light cast on the pathologic physiology of the small bowel in this disorder. The nontropical environment of the patients is worthy of mention. Nine of these patients came from the North Central States, one was from Texas. Two of the patients had been born in Northern Europe but had spent their adult lives in the United States. Five were women, and five were men. Their ages varied from 26 to 51 years, and the duration of symptoms varied from nine months to thirty years. In at least eight of the cases the condition was of a very chronic nature, symptoms having been in evidence for five or more years.

The principal clinical features of the disease as encountered in this series were (1) steatorrhea, with or without diarrhea, (2) gastrointestinal disturbances, (3) loss of weight and muscular wasting, (4) defective metabolism of calcium and phosphorus, leading in certain cases to tetany and osteoporosis, (5) physical stunting or rachitic stigmas and (6) anemia of various types and of various degrees of severity. Among the most remarkable features of the disease are the variability of the clinical picture and the tendency to remission and relapse. If one may judge from the literature, tropical sprue is fairly uniform in its manifestations, but this cannot be said of the so-called nontropical variety. Most of the literature on the subject of nontropical sprue consists of reports of one or two cases, and in a majority of these the attention of the author has been attracted to the most prominent individual clinical feature. This varies greatly in different cases and at different stages of the disease. As a result, the available descriptions of the disease are somewhat reminiscent of the well known description of the elephant by the group of blind men. In some cases the hematologic feature has apparently dominated the picture, in others the prominent feature has been the tetany, and in still other instances the gastro-intestinal disturbances have been particularly conspicuous.

The presenting symptoms in this series of cases are of interest in this connection. Weakness was mentioned eight times, it ranged from easy fatigability to actual adynamia. Diarrhea was mentioned an equal number of times. It varied in severity, in some cases there being two or three stools a day while in others defecation occurred "hourly." Four patients complained principally of tetany. Abdominal cramps and flatulent indigestion were the principal symptom in six cases. Four of the five women had amenorrhea, the fifth had passed the menopause.

The physical findings were equally variable. Physical stunting was a striking feature in five cases. Deformities of the bones, either rachitic or secondary to osteomalacia, were noted in three cases. All patients gave evidence of extreme loss of weight and of muscular wasting, which contrasted strongly with the flatulence and distention of the abdomen characteristic of the disease. Glossitis, with local areas of moderate atrophy of the tongue, was noted in six cases. Six patients had peripheral edema, and in three of the cases this feature was particularly conspicuous. Signs of latent or active tetany were also noted in six cases. One patient, who had the most marked changes of the bones of any in the group, had a cutaneous lesion strongly resembling pellagra, another had a dermatologic picture suggestive of acanthosis nigricans. Two patients had definite neurologic signs of subacute combined sclerosis of the spinal cord, and one of these also had definite peripheral neuritis.

To summarize, the striking symptoms were fatty diarrhea, with associated gastro-intestinal disturbances, weakness, pallor, loss of weight and evidence of defective calcium metabolism. The most characteristic physical signs were emaciation, muscular wasting, meteorism, cutaneous lesions, edema and tetany. Tables 1 and 2 give the significant features of each case. Seven of the cases have been reported previously, and the reader is referred to the original descriptions for complete details. The eighth case was reported separately by Weir and Adams,<sup>13</sup> cases 9 and 10 have not previously been reported. The laboratory findings in this group of cases deserve special mention.

#### SPECIAL EXAMINATIONS

*Blood*—Bennett<sup>10</sup> and his collaborators described three types of anemia associated with nontropical sprue: (1) the hypochromic or secondary type, (2) a hyperchromic type, in which the morphologic features of the formed elements of the blood are very closely related to those which are present in pernicious anemia, and (3) an erythroblastic type.

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13 Weir, J. F., and Adams, Mildred. Idiopathic Steatorrhea. Metabolic Study of a Patient, with Reference to the Utilization of Nitrogen and Fat, *Arch. Int. Med.* **56**: 1109 (Dec.) 1935.

resembling von Jaksch's disease Thaysen<sup>14</sup> emphasized the fact that the hematologic picture in any given case may not be constant and that changes from hypochromic to hyperchromic anemia may occur. He discovered that this was particularly true in cases in which the patient had undergone treatment. Five of this series of patients presented a hematologic picture closely related to and practically indistinguishable from that of primary anemia. Macrocytosis was a striking feature. The individual cells varied somewhat in their staining properties, however, and the changes in the leukocytes were not as definite as were those usually seen in primary anemia. Three patients had a hypochromic type of anemia, in two cases the blood smears were not studied sufficiently to permit accurate classification. In one of the latter cases (case 2) the volume index was 0.88, probably representing a secondary type of anemia. In the other case (case 3), the volume index was 1.03, which makes it seem likely that this case was an instance of hyperchromic anemia. One patient (case 9) had definite eosinophilia. The morphologic features of the formed elements of the blood in this series of cases parallels closely those observed by Fairley and his associates<sup>14</sup> in cases of tropical sprue. As will be disclosed later, there is good reason to believe that the anemia in this series of cases, although variable and not as marked as the usual form of primary anemia, is essentially a symptom of a deficiency disease and is most probably the result of deficient absorption of essential hematopoietic substances in the small intestine.

*Gastric Acids*—Free hydrochloric acid was present in the gastric contents at one time or another in every case. In case 3 the patient had been examined at the clinic before her acute illness, and the value for the gastric acids were found to be 20 for free hydrochloric acid and 32 for total acidity after an Ewald test meal (Topfer's method). During an acute exacerbation no free hydrochloric acid could be demonstrated, but stimulation with histamine was not employed to prove whether there was true achlorhydria. In case 4 the patient presented herself at the clinic originally with an active duodenal ulcer, and the values for gastric acids were found to be 48 for free hydrochloric acid and 62 for total acidity after an Ewald test meal (Topfer's method). Several weeks after gastro-enterostomy had been performed and during an acute exacerbation of the diarrhea, complete anacidity was noted, which persisted even after stimulation with histamine. In case 5 the patient originally had anacidity after an Ewald test meal, and at a somewhat later date the maximal values for gastric acids were 42 for free hydrochloric acid and 56 for total acidity (Topfer's method) after

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14 Fairley, N. H., Mackie, F. P., and Billimoria, H. S. Anaemia in Sprue. An Analysis of Sixty-Seven Cases, *Indian J. M. Research* 16: 831 (Jan.) 1929.

TABLE 1—Clinical Findings in Ten Cases of Nontropical Sprue

Case	Age in Years and Sex	Duration	Diarrhea	Infantilis	Edema	Bony Deformity	Tetany, Active or Latent	Glossitis	Loss of Weight		Amenorrhea	Pigmentation	Roentgen Examination of Intestinal Tract	Comment
									Pounds	Kg				
1	31 F	Lifelong, worse last 7 years	Episodic, grade 2 3	++		Rachitic stigmata	Active +++	Slight	45	20.4	+	Definite	None	
2	33 F	Lifelong, worse last 6 to 7 years	Episodic, lifelong	+		Marked osteomalacia	Active ++	None	40	18.1	+	Definite eruption resembling pellagra	None	
3	51 F	2 to 3 years, moderate		+		None	Active ++++	None	20	9.0	Past + menopausal	Urticaria, slight pigmentation	None	
4	47 F	20 years	1 episodic, 20 years	++	++	None	Seasonal active at times for 20 years	+	25	11.3	+	Slight	Jejunitis	
5	47 M	10 years plus	Episodic, 10 years	None	++	None	Active for 10 years	+	50	22.7		Slight	Jejunitis	
6	44 M	9 years	1 year grade 3	None	+	None	None	+	26	11.8		None	Jejunitis	
7	45 F	15 months	Grade 3	? Small frail type	++	None	Latent, one active attack	+	22	10.0	+	None, marked pruritus	Jejunitis and ileitis	
8	26 M	10 years	Grade 1 to 2	++	+	Rachitic stigmata, osteoporosis	None	+	20	9.0		Slight	Jejunitis and ileitis	
9	47 M	6 years	Occasional severe episodes grade 1 to 2	None	+	None	None	+	70	31.8		Lezema of hands, pigmentation	Jejunitis and ileitis	Indifferent response to treatment, death occurred at home, cause unknown
10	44 M	12 years	Slight, irregular	None	+	None	None	Slight	18	8.2		Extensive brownish pigmentation	Ileitis slight	Period of observation not sufficiently long for absolute diagnosis, good response to liver treatment

TABLE 2—Laboratory Findings in Ten Cases of Nontropical Sprue

Case	Age in Years and Sex	Hemoglobin, Erythrocytes, Leukocytes	Erythrocytes, Morphology	Gastric Acids, (Topfer's Method)	Stools	Serum Calcium, Mg in 100 Cc	Serum Phosphorus, Mg in 100 Cc	Serum Bilirubin, Mg in 100 Cc	Serum Protein, Mg in 100 Cc	Plasma Cholesterol, Mg in 100 Cc
1	31 F	54 3,620,000 6,800	Macrocytic anemia	Free HCl 40, total acidity 56	Oil or fat in excess	6.3 to 11.3	4.4 to 6.6			
2	33 F	54 3,370,000 2,700	Not examined, vol index 0.88	Free HCl 18, total acidity 38	Oil or fat in excess	6.3 to 8.2	2.3 to 4.5			
3	51 F	56 3,420,000 11,000	Vol index 1.03	Free HCl 20, total acidity 32, free HCl 0, total acidity 10	Fatty stools	1.9 to 7.7	2.4 to 4.6			
4	47 F	38 3,710,000 4,900	Hypochromasia	Free HCl 48, total acidity 62, anacidity later	Oil or fat in excess	6.3 to 11.6	1.0 to 1.1		11 to 5.0	139
5	47 M	64 4,000,000 6,500	Hypochromic anemia	Free HCl 42, total acidity 56, anacidity later	Oil or fat in excess	6.8 to 8.6	2.9 to 3.9		4.4 to 5.3	
6	44 M	64 3,250,000 5,100	Macrocytic anemia	Free HCl 58, total acidity 64, free HCl 18, total acidity 28	Oil or fat in excess	8.0 to 10.5	2.2 to 3.1			103
7	45 F	67 7,790,000 5,600	Macrocytic anemia	Free HCl 46, total acidity 58	Fat in excess	6.8 to 9.0	2.8 to 3.0		1.8 to 6.1	
8	26 M	62 2,580,000 2,700	Macrocytic anemia	Free HCl 22, total acidity 38	Fat in excess	7.8 to 8.7	3.5 to 4.9	1.1 to 1.3	1.9	93
9	47 M	50 2,850,000 2,300	Hypochromasia, eosinophilia	Anacidity at first, after stimulation with histamine, free HCl 36, total acidity 46	Fat in excess	8.5 to 10.1	3.6 to 4.2	1.0	5.6 to 5.9	
10	44 M	70 3,510,000 3,100	Macrocytic anemia	Free HCl 38, total acidity 50	No fat in excess with low fat diet	9.5	4.2		7.3	



stimulation with histamine. In case 9 also the patient had anacidity after an Ewald test meal, and the maximal values for gastric acids later were 36 for free hydrochloric acid and 46 for total acidity (Topfer's method) after stimulation with histamine. There was some evidence to suggest a reduction in the concentration of free hydrochloric acid in the gastric juice during acute exacerbations and restoration of normal values during remissions. The gastric secretions in this series of cases had about the same features as have been described in reports of cases of tropical sprue.

*Stools*—The stools were as a rule pale, voluminous, foul and obviously fatty and resembled those characteristic of the tropical variety of the disease, except that they were seldom foamy. They varied somewhat in frequency and volume in the individual cases and in the same case at different stages of the disease, but during periods of active diarrhea their appearance was fairly constant. Microscopic examination of stained specimens demonstrated the presence of oil or fat in excess. This feature of the disease has been carefully studied by Thaysen<sup>8</sup> and by Bennett and his collaborators, who demonstrated a high total percentage of fat, chiefly split or neutralized. In cases personally studied by Thaysen, the output of fat for twenty-four hours varied from 15.9 to 66.7 Gm., the average being about three times the normal excretion of fat. He also noted that about a third of the total amount of fat ingested was lost in the stools. Foamy stools, such as have been described in reports of cases of tropical sprue, were not a striking feature in any case in the present series. The total amount of fat in the stool was studied under controlled conditions in only one case, since it was felt that variations in the intake and excretion of fat under ordinary conditions probably rendered the fractional determination of the amounts of fats, soaps and fatty acids of the individual stools valueless. A more detailed consideration of the utilization of fat in one case, in which the patient was undergoing treatment, will appear later.

*Blood Calcium and Phosphorus*—The metabolism of calcium and phosphorus in the disease has been studied in detail by Aub and his associates<sup>15</sup> and by Bauer and Marble<sup>16</sup>. The concentrations of calcium

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15 Aub, J. C., Albright, Fuller, Bauer, Walter, and Rossmersl, Elsie. Studies of Calcium and Phosphorus Metabolism. IV. In Hypoparathyroidism and Chronic Steatorrhea with Tetany with Special Consideration of the Therapeutic Effect of Thyroid, *J. Clin. Investigation* **11** 211 (Jan.) 1932.

16 Bauer, Walter, and Marble, Alexander. Studies on the Mode of Action of Irradiated Ergosterol. II. Its Effect on the Calcium and Phosphorus Metabolism of Individuals with Calcium Deficiency Diseases. *J. Clin. Investigation* **11** 21 (Jan.) 1932. Marble, Alexander, and Bauer, Walter. Calcium and Phosphorus Metabolism in a Case of Nontropical Sprue with Associated Tetany, *Arch. Int. Med.* **48** 515 (Sept.) 1931.

and phosphorus in the serum are, in most instances, reduced. According to these authors, the urinary excretion of calcium is low but the fecal excretion of calcium is increased, they also reported a marked increase in the urinary excretion of phosphorus. The range of values for calcium and phosphorus in the blood serum of the individual patients in this series is given in table 2. Large variations were observed, depending on the stage of the disease and the severity of the diarrhea. During periods when the diarrhea was severe it was noted not only that there was a rapid decrease in the amount of calcium in the blood serum but that elevation in the level of calcium in the serum could be obtained only with difficulty, even by the use of parathyroid extract. This was particularly striking in case 3. During periods of improvement, when the diarrhea was under control, values for calcium and phosphorus in the serum tended to increase slowly, however, normal values were rarely obtained except during prolonged remissions.

These changes in the metabolism of calcium and phosphorus were obviously reflected in the clinical condition of the patient. During periods of acute loss of calcium, tetany, either active or latent, was a common feature. In case 2, latent tetany, with a reduction in the amount of calcium in the serum, persisted in spite of the employment of parathyroid extract and the administration of large amounts of calcium salts by mouth. In this particular case, however, the skeletal depletion of calcium was so great that little help could have been expected from any source. In case 4 the administration of parathyroid extract was of great value in controlling severe, active tetany, but the response to this preparation was less prompt than is usual, principally because of rather active diarrhea, with presumable loss of calcium from the organism.

In one case roentgenologic examinations of the long bones disclosed marked osteomalacia (case 2), with deformities of the pelvis and the long bones and pseudofractures. In two other cases (cases 6 and 8) definite osteoporosis was noted. In the whole group the skeletal changes were distinctly less prominent than they were in the cases reported by Bennett<sup>10</sup> and his collaborators. In this connection, it is of interest to note that tetany is uncommon in cases of tropical sprue, although low levels for calcium and phosphorus in the serum are the rule. Osteoporosis and osteomalacia are apparently even less frequently encountered.

*Roentgenologic Examination of the Small Intestine*—Roentgenologic examination of the small intestine was performed in seven of the ten cases under consideration. The findings have been reported separately by Camp<sup>11a</sup> and have been touched upon briefly in an earlier paper.<sup>11e</sup> My attention was attracted to the possible diagnostic value of such

examinations by the few records of necropsy in cases of this disease. In each of seven cases in which postmortem studies have been reported various degrees of atrophy and dilatation of the intestine were noted. It was therefore not particularly surprising that in seven of the cases studied by my associates and me some roentgenologic evidence of involvement of the small intestine was noted. Mackie<sup>9</sup> has also studied independently this aspect of the disease and reported similar roentgenologic findings.

The characteristic findings, as reported by Camp and me<sup>11e</sup> before the Minnesota Society of Internal Medicine (May 1933), are delayed motility and alterations in the mucosal relief of the small intestine, especially the jejunum, consisting of smoothing of the contours of the lumen, obliteration of the usual markings of the valvulae conniventes and clumping of the barium sulfate in elongated masses. The roentgenologic findings suggested the presence of edema of the mucosa and infiltration of the walls, involving especially the jejunum and the ileum and occasionally the duodenum and the colon. A moderate degree of megacolon was observed in two cases, and in two instances the general roentgenologic appearance of the colon suggested that which is seen in cases of ulcerative colitis, reexamination, however, eliminated this condition from consideration. It was interesting to note that in two cases in which there was an opportunity for repeated examination the roentgenologic evidence of disease in the small intestine became progressively less as the patient improved. In case 10 the gastrointestinal symptoms were not pronounced at the time of examination and a moderate degree of involvement of the ileum was noted. It is not believed that these findings are necessarily specific for nontropical sprue, since they may be present in varying degrees in association with other conditions of the intestinal tract and, in fact, have been noted in cases of pancreatic carcinoma. Their presence, however, constitutes tangible evidence of significant changes in the small intestine, which correspond grossly to the changes which have been noted at necropsy in cases of this disease.

*Miscellaneous Findings*—Fairley commented on the fact that the bilirubin content of the serum is normal in patients with tropical sprue and that this finding serves in part to distinguish the condition from primary anemia. In two cases in this series the amount of bilirubin in the blood serum was within normal limits and the result of the van den Bergh test was indirect. A low value for the cholesterol in the plasma was also mentioned by Fairley as a significant laboratory finding in cases of tropical sprue. In four cases in this series mild hypocholesteremia was noted (table 2). An attempt was made to study duodenal ferments in three cases, but on account of the poor condition of the

patient the results were entirely unsatisfactory in two of them. The results in one case (case 8) are noted in table 3. These figures, of course, indicate normal activity of lipase. Values for trypsin were normal or slightly reduced, those for amylase were definitely subnormal and perhaps correspond to the moderate intolerance for carbohydrate which may be a rather definite clinical feature of this disorder.

As has been mentioned, edema was a rather striking feature in several of these cases. It may be assumed that it was of nutritional origin and essentially identical with "hunger edema." The serum proteins were studied in the five cases under discussion, and it was noted that in each instance the content was definitely reduced, the average value lying at or near 5 Gm. for each hundred cubic centimeters of serum, the so-called "edema level." In some instances a gradual decrease in the amount of serum protein was noted during exacerbations of the diarrhea and a slow increase was present during remissions.

TABLE 3—*Duodenal Ferments in a Case of Nontropical Sprue*

Date, 1934	Trypsin, Units	Amylase, Units	Lipase	
			Ethyl Butyrate Substrate, Cc	Olive Oil Substrate, Cc
3/15	Less than 0.5	Less than 2		
4/7				
4/23			2.0, 2.3	12.4, 13.6

#### DIAGNOSIS

The clinical recognition of fully developed nontropical sprue should not be difficult if the condition is borne in mind. The combination of chronic steatorrhea, marked nutritional disturbances, anemia and disturbance of the metabolism of calcium should lead to a diagnosis in a majority of cases. Confirmatory evidence may be obtained by studies of the fat content of the stools, of the morphology of the formed elements of the blood, of gastric secretion and of the roentgenologic appearance of the jejunum and ileum. Pancreatic neoplasm, tuberculous enteritis and lymphadenitis and regional nonspecific ileitis must, of course, be excluded.

A demonstration of some morphologic or functional change in the small intestine is of considerable importance, since the underlying etiologic factor which appears to explain, tentatively at least, all the heterogeneous signs and symptoms of the disease is a failure of the normal absorptive functions of the intestine. As Fairley<sup>17</sup> said of sprue, this

<sup>17</sup> Fairley, N. H. Megalocytic Anaemia in the Tropics, with Special Reference to Sprue, *Proc. Roy. Soc. Med.* **25**: 1708 (Sept.) 1932.

is essentially a gastro-intestinal malady. The examination of the reports of cases which have appeared in the literature and of the records of the cases in this series seems to point to the existence of three types of the condition: (1) that which is characterized by marked anemia, chiefly of the hyperchromic variety, glossitis, moderate digestive symptoms and minimum changes in the metabolism of calcium and phosphorus, (2) that in which there are marked steatorrhea, tetany (active or latent) and depletion of the skeletal calcium of greater or lesser degree and (3) a combination type, in which the principal features of the first two types are associated. Of this series of ten cases, cases 7, 9 and 10 may be classified as instances of the first type (the condition in these cases corresponds closely with that in the group described by Reed and Ash<sup>18</sup> as instances of "atypical sprue"). In cases 1 to 6, inclusive, the disease was characteristic of the second type, and case 8 was an instance of the third type. It is difficult to escape the conclusion that there must be a considerable variability in intestinal absorption in these three types, the patients who have the most marked hematologic changes are particularly handicapped in their ability to utilize essential hemopoietic substance, and those with the second type are unable to absorb fat, calcium or vitamin D. It has not been possible to connect these variations with the involvement of any particular segment of the intestine, probably the differences in absorption are the result of functional rather than of anatomic variations. All the three types mentioned will be verified or disproved as additional cases are observed and reported, the distinction mentioned may be purely artificial and of no special significance. Studies on calcium and phosphorus balance during a period of therapy directed primarily toward the hematologic features in a case in which the patient has calcium deficiency and tetany should cast some light on this point.

#### PATHOGENESIS

Much has been written of the nature of both the tropical and the nontropical variety of sprue, and numerous hypotheses of etiology have been advanced. The evidence in favor of each of these was discussed by Thaysen in his recent monograph and also by Bennett and his collaborators. It has been suggested that the condition is a specific and perhaps an infectious type of disease of the small intestine, with secondary deficiencies in the absorption of fats, proteins, minerals, vitamins D and B<sub>12</sub> and certain substances essential to hemopoiesis. However, pathologic, bacteriologic or mycologic evidence to support the idea of a specific intestinal disease has not been forthcoming. The lesions that have been observed at necropsy suggest a degenerative

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<sup>18</sup> Reed, A. C., and Ash, J. E. Atypical Sprue, *Arch Int Med* **40** 786 (Dec.) 1927

rather than an infectious process,<sup>19</sup> and the theory advanced by Ashford,<sup>20</sup> that infestation with *Monilia* is responsible, has been largely discarded

A second theory holds that sprue is essentially a deficiency disease in the same sense as is pernicious anemia, the lesions observed in the small intestine being regarded in about the same light as is atrophic gastritis in the latter disease. In favor of this theory, the recently published studies of Rhoads and Miller<sup>21</sup> may be emphasized. These authors expressed the opinion that clinical sprue may arise in three ways: (1) by dietary deficiency of the extrinsic factor, (2) by lack of the same gastric enzyme that is absent in pernicious anemia and (3) by inability to absorb the product of interaction of the first two. It is assumed that differences in the relative importance of each factor may be responsible for variations in the clinical picture. These investigators feel that on this basis it is advisable to administer the product of the interaction of the gastric enzyme and the dietary factor (i.e., liver extract) in sufficient amounts to produce a remission. Their results following the administration of massive doses of liver extract parenterally in cases of tropical sprue certainly add much weight to this theory, and my experiences with parenteral liver therapy in this series of cases of the nontropical disease are confirmatory. Rhoads and Miller felt, as did Baumgartner and Case,<sup>22</sup> that the effects of dietary treatment are entirely a matter of supplying large amounts of water-soluble vitamin. The experimental study of Miller and Rhoads<sup>23</sup> is of interest in this connection; they produced in experimental animals a syndrome similar to sprue by the use of a diet deficient in vitamin B<sub>2</sub>. In their animals there developed stomatitis, vomiting and diarrhea,

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19 Blumgart, H. L. Three Fatal Cases of Malabsorption of Fat, with Emaciation and Anemia, and in Two Acidosis and Tetany, *Arch Int Med* **32** 113 (July) 1923. Salvesen, H. A. Observations on Human Tetany. I. Spontaneous Tetany in Adults, *Acta med Scandinav* **73** 511, 1930. Starr, Paul, and Gardner, Lois. A Biochemical Study of Two Patients with a Condition Simulating Sprue, *Am J Trop Med* **10** 283 (July) 1930. Whipple, G. H. A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues, *Bull Johns Hopkins Hosp* **18** 382 (Sept.) 1907.

20 Ashford, B. K. A Clinical Investigation of Tropical Sprue, *Am J M Sc* **165** 157 (Feb.) 1923.

21 Rhoads, C. P., and Miller, D. K. Intensive Liver Extract Therapy of Sprue, *J A M A* **103** 387 (Aug 11) 1934.

22 Baumgartner, E. A., and Case, C. E. Reticulocyte Response in a Case of Tropical Sprue on a Diet Not Including Liver, *Clifton M Bull* **16** 183 (Oct.) 1930.

23 Miller, D. K., and Rhoads, C. P. Production in Dogs of a Syndrome Similar to Sprue by Diets Deficient in Vitamin B<sub>2</sub>, *Proc Soc Exper Biol & Med* **30** 540 (Jan.) 1933.

with yellow, semisolid stools, marked loss of weight and anemia. It is also interesting to note that the anemia of sprue is relieved by yeast extracts, whereas primary anemia is unaffected by this treatment.

A third conception of the disease, which is perhaps more useful to physicians practicing in nontropical climates, is that the syndrome of sprue may not necessarily constitute a specific entity but may be produced by various diseases of the small intestine, by various deficiency states or by any condition which seriously interferes with absorption from the upper part of the intestinal tract. Fairley and Kilner<sup>24</sup> have demonstrated that gastrojejuno-colic fistula can produce symptoms closely comparable to those of sprue. We have recently observed a patient with carcinoma of the pancreas who presented many of the signs and symptoms of the syndrome of sprue, even to the roentgenologic evidence of involvement of the small intestine. Holst<sup>25</sup> and Brems<sup>26</sup> recently cited similar cases, and Greenberg<sup>27</sup> reported experiments with animals which indicate that the symptoms of celiac disease may be reproduced in part by excluding the external pancreatic secretions from the intestines of small animals.

For obvious reasons, it is impossible at this time to give a final statement as to the exact nature of nontropical sprue. The evidence in favor of a deficiency state is very strong and constitutes the best single explanation for the etiology of both the tropical and the nontropical form of the disease. Whether this deficiency is a primary or a secondary condition is as yet uncertain. Until further information in regard to the functional and anatomic disturbances of the small intestine in both conditions becomes available, the interrelation of the nontropical and tropical varieties of this syndrome will remain an unsettled problem.

Thaysen,<sup>12e</sup> who, because of his extensive studies in this field, may be regarded as an authority, expressed the opinion that celiac disease in children, tropical sprue and the nontropical variety of sprue are closely related, if not identical, and suggested grouping them under the head of "the coeliac affection." Further studies should serve to clarify the subject and may bring into relation with the "coeliac affection" some of the digestive deficiency syndromes, which are little understood.

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24 Fairley, N. H., and Kilner, T. P. Gastro-Jejuno-Colic Fistula, with Megalocytic Anaemia Simulating Sprue, *Lancet* **2** 1335 (Dec. 19) 1931.

25 Holst, J. E. Ein Fall von pankreatogener Steatorrhoe, *Ztschr. f. klin. Med.* **115** 286, 1930.

26 Brems, A. Ein Fall von pankreatogener Fettdiarrhoe, *Acta med. Scandinav.* **78** 80, 1932.

27 Greenberg, Jacob. An Attempt to Reproduce Coeliac Disease Experimentally in Young Animals by Excluding the External Pancreatic Secretion from the Intestine, *Yale J. Biol. & Med.* **6** 121 (Dec.) 1933.

certain obscure types of anemia and conditions associated with abnormalities of the metabolism of calcium and phosphorus

#### TREATMENT

As is usual in connection with diseases subject to spontaneous remissions, a large number of therapeutic measures, dietary and otherwise, have been recommended for both tropical and nontropical sprue. Since the basic difficulty seems to be primarily a matter of deficient utilization of fat, minerals, vitamins and other essential elements of diet from the small intestine, it appears that measures directed toward the digestive phases of the disorder are of some importance. As Thaysen<sup>8</sup> pointed out, three different dietetic programs have been recommended, each of which is based on a preponderant use of one of the food elements and each of which has apparently given good results in the hands of certain investigators. Among the diets recommended are the following: (1) a puréed diet of varying composition, (2) a diet that is high in fats and low in protein and (3) a fruit diet, particularly one composed chiefly of bananas. These diets have been designed to spare the intestinal tract so far as is possible during acute exacerbations of the disease. In the majority of cases of this series there was a definite intolerance to fat, and diets which contained a large amount of fat usually increased the diarrhea and other gastro-intestinal symptoms. The graduated type of diet, which is high in protein and low in fat, as advised by Fairley,<sup>28</sup> has been satisfactory in clinical use, but it is not apparent that the ability of the patient to absorb fat has been greatly increased by the use of such diets.

The administration of calcium in some form is obviously indicated especially in those cases in which the values for calcium in the serum are reduced and in which there are tetany and osteoporosis. The administration of vitamin D in some form, preferably viosterol, appears to facilitate greatly the absorption of calcium. Investigators<sup>29</sup> have demonstrated a definite storage of calcium and phosphorus when viosterol was administered, and Linder and Harris<sup>30</sup> claimed that no special dietary regulation is necessary if vitamin D is administered in sufficient quantity. This certainly does not apply to all cases, but it may be true in those in which deficiency of calcium dominates the picture. Parathyroid extract has been used by a number of investigators in the treatment of this disease. As has been previously disclosed, it does not produce a significant elevation of the amount of calcium in the blood.

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28 Fairley, N. H. Sprue. Its Applied Pathology, Biochemistry, and Treatment, *Tr. Roy. Soc. Trop. Med. & Hyg.* **24** 131 (Aug.) 1930.

29 Anderson and Lyall<sup>12a</sup> Bowen-Davies<sup>12b</sup> Ashford<sup>20</sup>

30 Linder, G. C., and Harris, C. F. Calcium and Phosphorus Metabolism and Chronic Diarrhoea with Tetany, *Quart. J. Med.* **23** 195 (Jan.) 1929.



serum in the presence of marked osteoporosis or during exacerbations of the disease, when the diarrheal symptoms are severe. It is perhaps best to confine its administration to patients who have severe tetany (chart 1), and the treatment should be discontinued as soon as the convulsive seizures are under control. To continue its administration over longer periods invites further depletion of the calcium that is stored in the skeleton.

Castle and Rhoads<sup>31</sup> discovered that liver extract usually induces prompt remission of tropical sprue. The hyperchromic variety of anemia associated with the nontropical types of the disease appears to respond in a specific manner to the administration of liver extract, especially

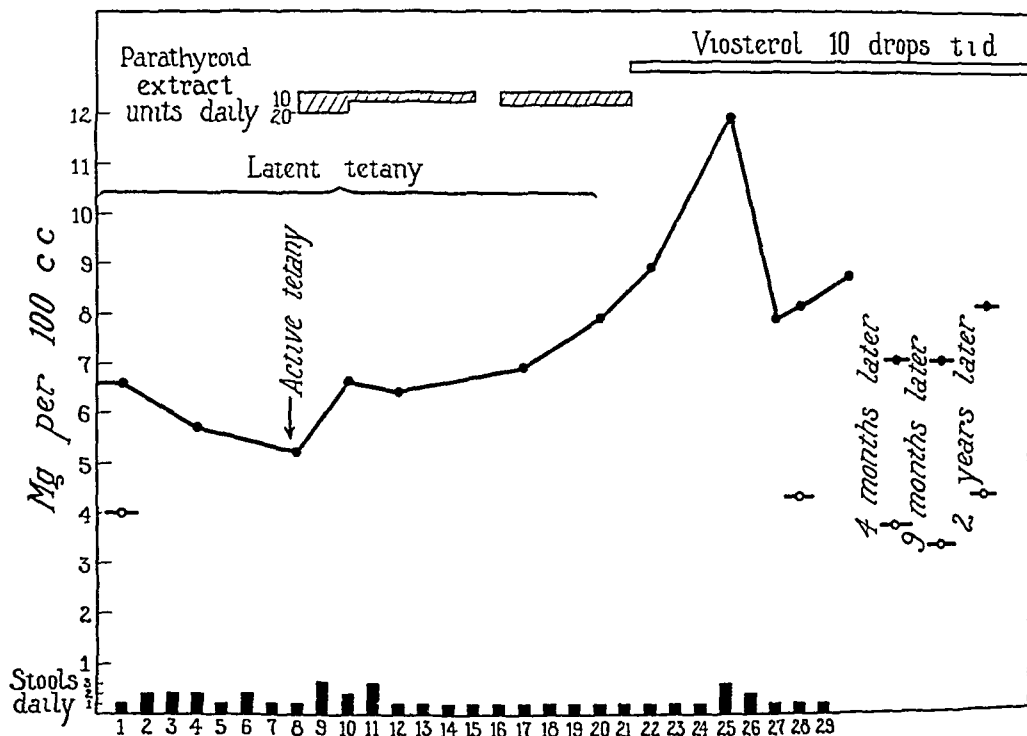


Chart 1—Calcium and phosphorus content of the blood in a case of nontropical sprue in which there was tetany. The amounts of calcium are indicated by the solid line with solid dots. The amounts of phosphorus are indicated by the open circles. The shaded blocks indicate the periods during which parathyroid extract was administered, the number of units given daily being indicated by the figures.

if it is administered parenterally, the glossitis, the gastro-intestinal symptoms and the systemic manifestations of the disease are also favorably affected. Porter and Rucker<sup>32</sup> reported good results in their cases from the use of liver extract without dietary or other treatment.

31 Castle, W. B., and Rhoads, C. P. The Etiology and Treatment of Sprue in Porto Rico, *Lancet* **1** 1198 (June 4) 1932.

32 Porter, W. B., and Rucker, J. E. The Treatment of Nontropical Sprue with Liver Extract. Report of Two Cases, *Am J M Sc* **179** 310 (March) 1930.

In cases of the more severe type the parenteral method of administration seems preferable because of the fact that absorption in the intestinal tract may be retarded. In cases 7, 8, 9 and 10 in this series the patient responded satisfactorily to the parenteral administration of liver extract, and in case 5 the patient was much benefited by the oral administration. A number of other patients in the series have taken liver extract by mouth in small and perhaps insignificant quantities and have also had various amounts of cooked liver in the diet, with indifferent therapeutic results. Thaysen pointed out that the hyperchromic type of anemia may change to the hypochromic or secondary variety under treatment and also commented on the fact that the latter variety of anemia may persist even after liver therapy. In such cases, iron in some form has been used to good effect. Castle and Rhoads made a somewhat similar observation in cases of tropical sprue. Marmite, a hydrolized yeast extract, has also been recommended enthusiastically by certain investigators,<sup>33</sup> the effects obtained being undoubtedly the result of the vitamin B<sub>2</sub> that it contains. Those who have had large experience with liver treatment are inclined to feel that it constitutes almost a specific remedy for the tropical variety of sprue, if used in adequate dosage, and feel that there is little necessity for dietary treatment if adequate liver therapy is employed. My own experience has not been sufficient to warrant an opinion, but in general it seems that some type of dietary regulation and the administration of calcium salts and viosterol is necessary, because of the disturbed absorption of calcium, which has been such a conspicuous feature in certain cases, and also because of the marked digestive symptoms.

Perhaps the best illustration of the effect of treatment in this series was encountered in case 8.

A man aged 26 came to the clinic because of chronic diarrhea, glossitis, weakness, paresthesia of the extremities and edema. Physical examination disclosed muscular wasting, meteorism, pallor, edema and subacute combined sclerosis of the spinal cord. The significant laboratory findings included a hyperchromic variety of anemia, a reduction of the amount of protein, calcium and phosphorus in the blood serum and definitely fatty stools.

The patient was intelligent and cooperative and readily agreed to become the subject of a metabolism study to determine his ability to utilize fat and nitrogen. He was given a daily diet composed of 80 Gm of protein, 44 Gm of fat and sufficient carbohydrate to furnish an energy value of approximately 1,800 calories. The stools and urine were collected in the usual manner, the nitrogen balance was determined, and the amount of fat excreted was compared with intake of fat. Liver extract was given parenterally in doses of 3 cc on each of four successive days. During the first two four day periods of observation the nitrogen

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<sup>33</sup> Vaughan, Janet M., and Hunter, Donald. The Treatment by Marmite of Megalocytic Hyperchromic Anemia Occurring in Idiopathic Steatorrhea (Coeliac Disease), *Lancet* 1 829 (April 16) 1932.

balance was strongly positive, about 35 Gm of nitrogen being stored daily. An average of about 12 Gm of fat was lost daily, but more than 30 Gm of fat was utilized. During the third four day period viosterol and calcium lactate were also administered, but the absorption of fat was not affected significantly. The nitrogen balance remained positive, about 25 Gm being retained daily in this period. During the fourth period of four days, he was given a daily diet which consisted of 101 Gm of protein, 50 Gm of fat and sufficient carbohydrate to fur-

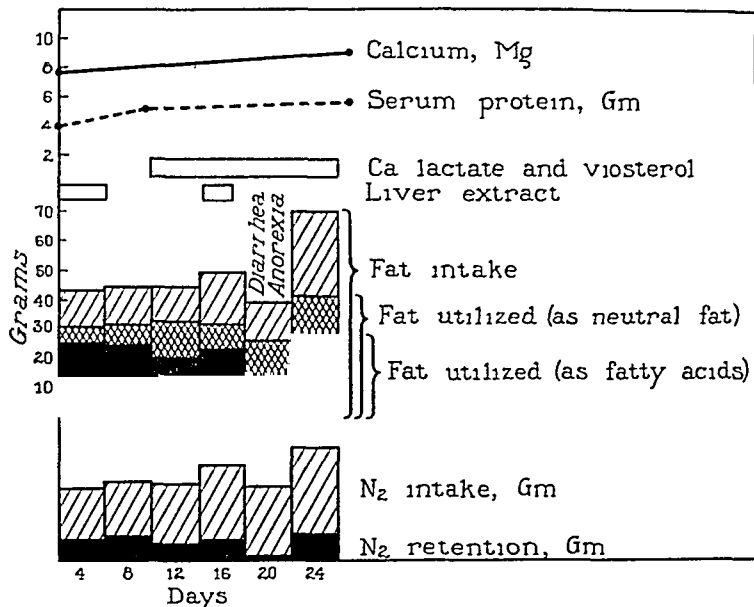


Chart 2—Retention and utilization of fat and nitrogen in a case of nontropical sprue

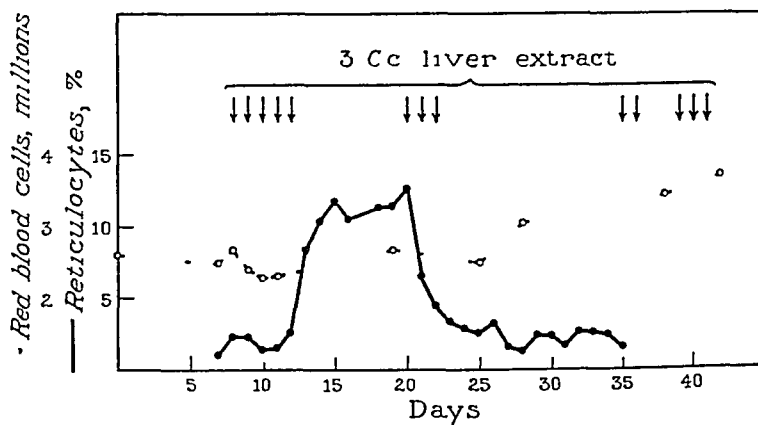


Chart 3—Changes in the percentage of reticulocytes and in the number of red blood cells presumably occurring as a result of the administration of liver extract

nish approximately 2,080 calories. The positive nitrogen balance increased to an average of 37 Gm daily, but no more fat was utilized, practically all the added fat being eliminated in the feces. The fifth period was marked by a transient gastro-intestinal disturbance, which was characterized by nausea, vomiting and some diarrhea. As a result of this, the positive nitrogen balance fell to 07 Gm daily and the absorption of fat was moderately reduced. During the sixth

period, the diet was as follows protein 122 Gm, fat 70 Gm and sufficient carbohydrate to furnish approximately 2,646 calories Calcium lactate and viosterol were given as before During this period the positive nitrogen balance reached the high figure of 4.6 Gm daily and the utilization of fat averaged 41 Gm a day Marked improvement took place during this entire period, and the diet was kept constant for about a month The condition of the patient during this period was probably improved further by another series of three parenteral injections of 3 cc of liver extract on successive days The weight of the patient did not greatly increase at first, principally because of the fact that he lost a great deal of edema fluid during the later periods of the investigation There was, however, definite increase in the amounts of calcium and protein in the serum during the whole period The retention and utilization of fat and nitrogen are illustrated graphically in chart 2 The changes in the number of reticulocytes and erythrocytes, presumably occurring as a result of liver therapy, are shown in chart 3 The improvement in the hematologic condition corresponds grossly to that seen in pernicious anemia following the use of liver extract Two months later the patient was still in good health, had gained considerable weight and was free from diarrhea

It should be stated parenthetically that the response to treatment is not always so prompt or so satisfactory, the case reported by Mackie illustrates this point very well, and I have had similar difficulties, notably in case 7 of this series As Rhoads and Miller indicated, there is probably a threshold which must be exceeded if liver therapy is to be effective The best therapeutic results have been obtained in cases in which the patient was cooperative and willing to submit readily to changes in diet and medication and to tolerate a certain amount of discomfort from these sources Complicating gastro-intestinal factors, such as gastro-enterostomy in case 4 of this series and duodenal stenosis in the case reported by Radl and Fallon,<sup>34</sup> also add to the difficulties of treatment As in cases of tropical sprue, there is a definite tendency to relapse, and it is well to remind the patient that immediate good results do not necessarily mean freedom from trouble in the future

#### PROGNOSIS

The prognosis of nontropical sprue in the advanced stage depends on the degree of malnutrition existing at the time of its discovery, the thoroughness with which treatment can be carried out and the presence or absence of complicating disease There have been three deaths in this series of ten cases One patient (case 2) died of an intercurrent infection of the respiratory tract, another patient (case 7) died of a hemorrhagic disorder of unknown etiology, suggesting acute leukemia, the third (case 9) had an illness details of the terminal phase of which suggest an aplastic type of anemia All these deaths occurred elsewhere than at the Mayo Clinic, and in no instance was

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<sup>34</sup> Radl, R. B., and Fallon, Madelein. Nontropical Sprue with Duodenal Involvement and Tetany, *Arch Int Med* **50** 595 (Oct) 1932

necropsy performed Of the remaining seven patients, five are in good condition, the other two were unable or unwilling to continue treatment and have passed from observation In Bennett's series of cases the prognosis as to life appeared to be good, but because of the extensive skeletal lesions (osteomalacia) in several of his cases, a return of the patient to normal health could hardly be expected Injections of liver extract at intervals of from five to ten days may be required during the stationary periods of the disease, to insure against relapse Chronic states of calcium deficiency likewise require continuous attention if relapse is to be avoided

#### SUMMARY

A series of ten cases in which the clinical features of a syndrome resembling sprue were present is described The condition so closely approximated the tropical variety of the disease that a close etiologic relation is suggested In these and in other cases of such nontropical disease recorded in the literature, the disturbance in calcium metabolism (osteoporosis, tetany) was more pronounced than it has been in the reported cases of tropical sprue, the steatorrhea, the hematologic features and the evidence of a lesion of the small intestine were, however, similar to those noted in true sprue The response to liver therapy indicates a probable deficiency state similar to that which is present in persons with primary anemia, the clinical picture being complicated by a defective absorption of fat and minerals and probably of vitamin-containing components of the diet

EFFECT OF TOTAL THYROIDECTOMY IN MAN  
LABORATORY STUDIES AND OBSERVATIONS OF CLINICAL EFFECTS  
IN THIRTY-NINE CASES

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The considerable number of publications regarding total thyroidectomy for the relief of cardiac disease have thus far largely been concerned with the basic physiologic reasoning which indicates the desirability of the procedure, the historical background which has steadily linked together thyroid function and cardiac action, the technic of the surgical operation and the clinical benefit to patients on whom the procedure has been carried out. With the clinical reports have appeared such laboratory data as can be utilized to measure either the changed cardiac function or the altered thyroid function<sup>1</sup>

Coincident with these primarily clinical studies, there have appeared in fragmentary form a few articles dealing with the altered mechanism of the body apart from the changes commonly conceived as dependent

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From the surgical laboratories of the Peter Bent Brigham Hospital and the Harvard Medical School

1 (a) Blumgart, H L , Levine, S A , and Berlin, D D Congestive Heart Failure and Angina Pectoris The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity, *Arch Int Med* **51** 866 (June) 1933 Levine, S A , Cutler, E C , and Eppinger E C Thyroidectomy in the Treatment of Advanced Congestive Heart Failure and Angina Pectoris, *New England J Med* **209** 667, 1933 Cutler, E C , and Schnitker, M T Total Thyroidectomy for Angina Pectoris, *Ann Surg* **100** 578, 1934 Weinstein, A A , Davis, D , Berlin, D D , and Blumgart, H L The Mechanism of Early Relief of Pain in Patients with Angina Pectoris and Congestive Failure After Total Ablation of Normal Thyroid Gland, *Am J M Sc* **187** 753, 1934 Blumgart, H L , Riseman, J E F , Davis, D , and Berlin, D Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris, *Arch Int Med* **52** 165 (Aug ) 1933 Shambaugh, P , and Cutler, E C Total Thyroidectomy in Angina Pectoris An Experimental Study, *Am Heart J* **10** 221, 1934 Eppinger, E C , and Levine, S A The Medical Care of Patients Following Total Thyroidectomy, *J A M A* **102** 2076 (June 23) 1934 Blumgart, H L , Berlin, D D , Davis, D , Riseman, J E F , and Weinstein, A A Treatment of Angina Pectoris and Congestive Heart Failure, *Ann Int Med* **7** 1469, 1934

on athyroidism and some physiologic experiments stimulated by the clinical studies. It seemed to us that a grouping of all the data which have been compiled in the study of athyroid persons might be of general value, though chiefly significant to those concentrating on endocrinology.

It is true that when the work commenced our chief hope lay in bringing forward this new method of therapy, but we were also greatly concerned with possible undesirable sequelae, and therefore our pre-operative and postoperative studies were as complete as possible. At the same time that clinical and laboratory observations were made on the basal metabolic rate, the cholesterol level and the functional capacity of the heart before and after the operation, a great number of studies were made on the patients with the expectation that the removal of an important ductless gland might create changes which before operation we could not foresee. Thus we could imagine that the removal of a complete unit from the intricate composite interrelationship of the endocrine system might well affect the functions of other glands than the one removed. Our intention is to record all our clinical and laboratory observations, more as a physiologic study than because of their bearing on cardiac disease. We shall not consider primarily the relief from pain in angina pectoris or the restoration of compensation in valvular or myocardial heart disease but shall present the scientific data as records of what happens in man under the alteration of physiologic processes imposed through total thyroidectomy. Since the observations in many instances were repeated at frequent intervals and in some cases extended over a year, we are able to present data on observations made before thyroidectomy and during myxedema and on the changes that followed the administration of thyroid extract. Some of these data will have practical clinical application, some of them are understandable in relation to present-day endocrine knowledge, but some of them must be presented merely as scientific information, the explanation for which is still a mystery.

#### THE MATERIAL

The material for study included the cases of 22 patients with angina pectoris, 15 with chronic valvular heart failure (including 1 with chronic myocarditis with failure) and 2 with diabetes mellitus, with gangrene of the lower extremity, on whom total thyroidectomy was performed. As in all clinical work, complete examination could not be carried out on all the patients, since some could not, and a few were unwilling, to cooperate to the fullest extent. Others came to the hospital from outlying districts and did not return at the correct times for follow-up studies. Nevertheless, sufficient data were collected to permit us to report reliable conclusions. The cases used for this study are 39 of the 64 cases in which total thyroidectomy was performed at this hospital between December 1932 and December 1934. The data on the cases not utilized were insufficient or lacking in control information to be of value in this type of report.

Observations were made on the basal metabolic rate, volume of blood flow, vital capacity, temperature of the skin, mental reactions and changes in the body

weight, and on the following constituents of the blood cholesterol, calcium, phosphorus, protein, potassium, iodine and sugar

The determinations were made (a) just prior to operation, (b) within one week after operation, (c) when myxedema was setting in (later postoperatively), (d) during myxedema and (e) after thyroid therapy was instituted. Such an arbitrary division was made to observe the effect of the operation on the aforementioned functions of the body as well as to show the trend of these functions as myxedema set in and after the patient received thyroid substance. The physical condition of the patient with cardiac failure is distinctly different from that of the patient having angina pectoris, so the two groups will be discussed separately. In no instance was there a patient with cardiac failure with pain in whom the condition could be termed angina pectoris, and likewise no patient with angina pectoris showed any well marked sign of cardiac failure. Except for the pain and some evidence of coronary disease, patients in the group with angina pectoris may be said to be representative of persons in that respective age group.

The patients in both groups with cardiac disease were studied completely before operation, the completion of the various tests requiring about one week. Those in the group with cardiac failure were treated by the usual medical methods, including the administration of digitalis and diuretics, in an effort to build up the cardiac reserve. No attempt at dietary restriction was made, all patients receiving the usual hospital diet, with the exception of limitation of fluids in some cases. None of the patients studied was unduly obese, so that the results of studies of basal metabolism and vital capacity are comparable for each group. There were no known instances of endocrine dysfunction particularly referable to the pituitary gland or the pancreas in the groups with cardiac disease. Most notable was the absence of any dysfunction of the thyroid gland, as determined by observation of symptoms and studies of basal metabolism made before operation. Furthermore, histologic study of all the thyroid glands removed at operation showed them to be essentially normal.

The immediate postoperative studies were made usually between the fourth and the sixth days after operation, after the postoperative reaction had subsided and the patient was again receiving a full diet.

As clinical myxedema developed, the determinations were somewhat variable, since when the patient showed the first signs and symptoms of athyroidism he was usually given thyroid therapy. Therefore, we do not know what changes might have been noted in patients with complete myxedema. In some instances it was not necessary to allow marked myxedema to develop to gain relief from symptoms, so thyroid therapy was begun early. This discussion will therefore attempt to show only the general trend of the changes in body functions as we determined them through the cycle from the normal state toward myxedema and back toward normal.

#### BASAL METABOLIC RATE

The fall in the basal metabolic rate is the generally accepted criterion to substantiate the diagnosis of myxedema,<sup>2</sup> although it is now known that persons with pituitary adenoma (chromophobe or basophil) have an associated low basal metabolic rate.<sup>3</sup> The basal metabolic rate was

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2 Sturgis, C. C. Myxedema with Observations of Basal Metabolism, *M Clin North America* 5 1251, 1922.

3 Cushing, H. "Dyspituitarism" Twenty Years Later with Special Consideration of the Pituitary Adenomas, *Arch Int Med* 51 487 (April) 1933.



used in our study to determine the degree of myxedema when the patient showed the usual clinical signs

In 24 patients with angina pectoris the average basal metabolic rate before operation was  $-1.2$ , with extreme limits of  $-1.5$  and  $+1.3$ . This was not altered appreciably within one week after operation, when the average rate for the same group was  $-2$ , with limits of  $-2.1$  and  $+1.4$ . It required an average of nine and nine-tenths weeks for clinical myxedema to be established, the extreme limits being two and five-tenths weeks and twenty-four weeks. Three patients required nineteen, twenty-two and twenty-four weeks to reach the levels of  $-2.5$ ,  $-2.1$  and  $-2.0$ , respectively, this delay being attributed to the possible presence of aberrant thyroid tissue.

The average basal metabolic rate for the group (22 patients) after operation (in beginning myxedema) was  $-2.8$ . This relatively high figure, as stated previously, is due to the fact that marked myxedema did not develop in some patients after total thyroidectomy, and others received thyroid therapy before marked myxedema developed. In a series of 120 determinations of the metabolism of the 22 subjects we observed that when marked myxedema was allowed to develop the basal metabolic rate averaged more nearly  $-3.0$ . Following the administration of thyroid substance, the rate was elevated to an average of  $-1.5$ , though this is not the usual optimum level for these patients.

The average optimum level is about  $-2.0$ . Determinations made during periods of optimum symptomatic relief showed a relatively constant figure for a given patient. A certain individuality existed, however, so that we could not arbitrarily place the rate for all patients at  $-2.0$  and expect the best results. For instance, the condition of a given patient might be improved at this level, but he might have even more definite relief with a rate 5 or more points lower. On the other hand, since myxedema is obviously a pathologic state, it was deemed advisable to keep the patient as nearly free from it as possible without causing a return of symptoms. Therefore, if the symptomatic relief at  $-1.5$  was equal to that at  $-2.0$ , it was obviously better to keep the basal metabolic rate at the higher level. We were thus able in some cases to raise the basal metabolism to a normal level ( $+3$ ,  $-9$ ,  $-5$  and  $-4$ ) without a return of symptoms. There was great individual variation in the response to thyroid substance, although we noted in general that the rate for most patients could be maintained at a fairly fixed level of myxedema ( $-2.0$ ) with 0.015 Gm ( $\frac{1}{4}$  grain) of thyroid extract<sup>4</sup>.

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4 The brand of thyroid extract used conformed in potency to the requirements of the United States Pharmacopeia.

daily Means<sup>5</sup> observed in a study of 50 cases of spontaneous myxedema that a ration of 0.03 Gm ( $\frac{1}{2}$  grain) of thyroid daily was required to maintain a level of myxedema at —20

In the group with cardiac failure the average immediate preoperative basal metabolic rate in 15 patients was +3.1 per cent (limits —9 and +22), a higher level as compared with the more normal group with angina pectoris. Five of the 15 (33 per cent) had a basal metabolic rate of +13 or more, an elevation not uncommon in persons with 'cardiac decompensation'.<sup>6</sup> There was, however, a greater variation in this group immediately following operation, the average being —5, with limits of —22 and +12. The average time required to establish clinical myxedema was eight and five tenths weeks, with extreme limits of two and sixteen weeks. In the group with myxedema the basal metabolic rate averaged —27. Since a more marked state of myxedema is optimum for the group in which compensation is achieved by lowering the basal metabolic demands on the circulation, nearly the full-blown picture was allowed to develop in the majority. Following thyroid therapy the average basal metabolic rate was —11.2 per cent, although a level of more pronounced clinical myxedema was maintained than the figure indicates. Such an increased metabolic rate is compatible with the decreasing vital capacity that develops in these patients, particularly if they receive too much thyroid substance and decompensation again occurs.

#### CHOLESTEROL CONTENT OF THE BLOOD<sup>7</sup>

As the basal metabolic rate falls in persons with myxedema, the cholesterol content of the blood usually rises, causing a state of hypercholesteremia. Hurxthal<sup>8</sup> expressed the opinion that the cholesterol content of the blood is a definite function of the thyroid state and that it is an aid in the diagnosis of dysthyroidism. We observed a definite rise in the cholesterol level as myxedema was established. In the group with angina pectoris the average preoperative cholesterol content of the plasma for 23 patients was 256 mg per hundred cubic centimeters of blood. The figure is slightly elevated because it includes

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5 Means, J. H., and Lerman, J. The Symptomatology of Myxedema. Its Relation to Metabolic Levels, Time Intervals, and Rations of Thyroid, *Tr. A. Am. Physicians* **49**: 214, 1934.

6 Peabody, F. W., Wentworth, J. A., and Barker, B. I. The Basal Metabolism and the Minute-Volume of Respiration of Patients with Cardiac Disease, *Arch. Int. Med.* **20**: 468 (Sept.) 1917.

7 Bloor, W. R., Pelkan, K. F., and Allan, D. M. The Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, *J. Biol. Chem.* **52**: 191, 1922.

8 Hurxthal, L. M. Blood Cholesterol in Thyroid Disease. Effect of Treatment, *Arch. Int. Med.* **52**: 86 (July) 1933.

the values for 3 patients with initial hypercholesteremia (406, 415 and 470 mg, ages 42, 61 and 56 years, respectively) the cause of which could not be ascribed to diabetes, nephrosis or arteriosclerosis<sup>9</sup> By omitting the values for these 3 patients, the average for 20 patients was 230 mg per hundred cubic centimeters, with limits of from 100 to 325 mg per hundred cubic centimeters (average age, 58.7 years) The average immediate postoperative value for cholesterol was 248 mg per hundred cubic centimeters for the 23 patients Further determinations were made as the patients showed signs of myxedema, this brought with it a rising value for plasma cholesterol, reaching an average of 404 mg just prior to the administration of thyroid substance This is not an average of the highest cholesterol values In some cases the peak of the cholesterol value was reached several weeks before the basal metabolic rate was lowest, in other cases the cholesterol reached its highest value shortly after thyroid therapy was instituted An average of the highest values for cholesterol was 475 mg per hundred cubic centimeters, with limits of 275 and 744 mg The values after thyroid therapy were variable, depending on the patient's response to the administration of thyroid substance, but in general it can be stated that there was a fall of the cholesterol content toward normal, and when the basal metabolic rate was brought back to normal limits the cholesterol content also returned toward its preoperative level

The values for plasma cholesterol of the group with cardiac failure were similar to the foregoing values, except that no instance of hypercholesteremia was encountered preoperatively, possibly because such a condition occurs in a younger age group (average age, 39.9 years) The average value for twelve patients before operation was 182 mg per hundred cubic centimeters This rose to an average of 315 mg with myxedema As in the group with angina pectoris, there was in the group with cardiac failure a variation in the cholesterol content following thyroid therapy, with a similar trend toward normal following the administration of thyroid substance

#### RECIPROCAL CHOLESTEROL VALUES AND BASAL METABOLISM

That an inverse ratio exists between the basal metabolic rate and the cholesterol content of the blood in persons with hypothyroidism is borne out in our study of 35 patients, including 191 observations This would seem to confirm the statement of Cutting<sup>10</sup> that "the cholesterol

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9 Bruger, M, and Poindexter, C A Relation of Plasma Cholesterol to Obesity and to Some of the Complicating Degenerative Diseases, *Arch Int Med* **53** 423 (March) 1934

10 Cutting, W C, Rytand, D A, and Tainter, M L Relationship Between Blood Cholesterol and Increased Metabolism from Dinitrophenol and Thyroid, *J Clin Investigation* **13** 547, 1934

correlation is some function of a thyroid hormone" In the absence of a functioning thyroid gland the basal metabolism falls below normal, and the cholesterol content rises above normal in an inverse ratio, but this does not necessarily occur simultaneously, nor can the ratio be expressed on an absolute mathematical basis Of our 35 patients, 11 (31.4 per cent) showed a rapid fall in basal metabolism after total thyroidectomy, whereas the rise in cholesterol values occurred shortly thereafter (several weeks) Conversely, 9 patients (25.8 per cent) showed a rapid rise in the cholesterol content following the operation, with a fall in metabolism later In 15 cases (42.8 per cent) the fall in basal metabolism and rise in cholesterol content were simultaneous As a criterion for treatment of patients with hypothyroidism we agree

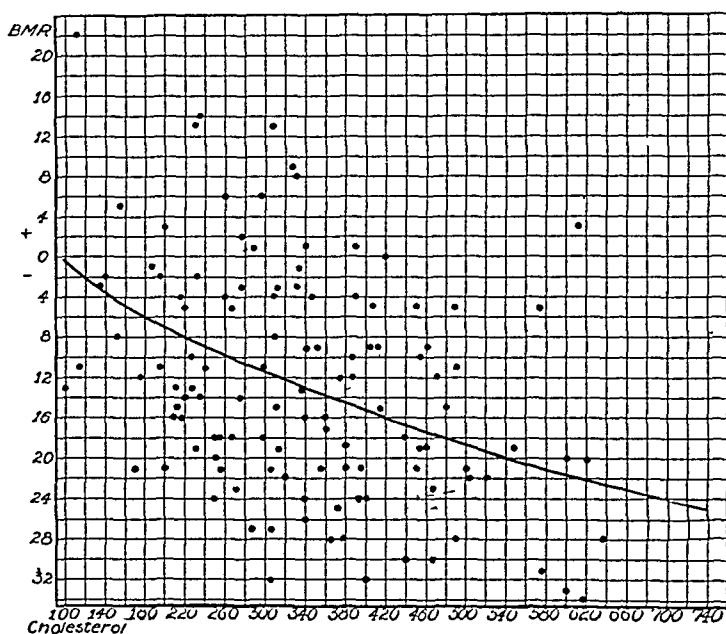


Chart 1—Ratio of the metabolic rate and the cholesterol content of the blood after thyroidectomy, based on 120 observations on twenty-two patients with angina pectoris

with Mason, Hunt and Hurxthal<sup>11</sup> that the cholesterol content is a better indicator of the severity of the disease than is the basal metabolic rate and is therefore a more accurate index for therapy This is probably due to the numerous sources of error which occur in determinations of the basal metabolic rate We had 4 patients who throughout their entire course showed normal readings for the basal metabolic rate (+3, -9, -5 and -4, respectively), their only indication of myxedema on laboratory examination being the rise in the cholesterol content (610,

11 Mason, R. L., Hunt, H. M., and Hurxthal, L. M. Blood Cholesterol Values in Hyperthyroidism and Hypothyroidism Their Significance, New England J. Med. **203** 1273, 1930

461, 573 and 390 mg, respectively) Chart 1 indicates the ratio of metabolism and cholesterol after thyroidectomy in the 22 cases of angina pectoris in which the basal metabolic rate and the values for cholesterol were normal before the thyroid gland was removed

In the state of myxedema just prior to the inception of thyroid medication, the average basal metabolic rate in all cases was  $-24.9$ , with an average value for cholesterol of 359 mg per hundred cubic centimeters Thyroid therapy tended to lower the cholesterol content as well as to raise the basal metabolic rate toward normal It appeared that the basal metabolic rate returned toward normal more rapidly than did the cholesterol value in most of the cases following the administration of thyroid substance

#### VITAL CAPACITY

The vital capacity of the lungs was determined in all cases with the patient in a sitting position in bed in an attempt to standardize the procedure for a basis of comparison The figures given are an average of three determinations made at one sitting The Collins vital capacity spirometer was used

The preoperative determinations for the group with angina pectoris were all slightly below normal (as compared with the standards of Bowen<sup>12</sup>) Immediately after total thyroidectomy<sup>13</sup> there was a striking decrease in 50 per cent of the cases, followed by a rapid recovery within seven days<sup>14</sup> In the remaining 50 per cent of the cases there was no alteration at this time Subsequent determinations for all the patients in the group after myxedema was established and after thyroid therapy showed essentially the same vital capacity as was noted preoperatively Hence, the myxedema following the total removal of a normal thyroid gland in a patient with angina pectoris causes no appreciable alteration of vital capacity This is in marked contrast to the study made by Blumgart, Gargill and Gilligan,<sup>15</sup> who noted that the vital capacity of the lungs was strikingly diminished in patients with spontaneous myxedema in the absence of any signs of congestive failure and did not show a significant change following treatment

The observations on the group with cardiac failure, however, were subject to variations Determinations of vital capacity were made immediately after the patient was admitted to the hospital, and it was noted that 5 of the 14 patients (36 per cent) had a vital capacity below 45

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12 Bowen, B D Relation of Age and Obesity to Vital Capacity, *Arch Int Med* **31** 579 (April) 1923

13 All the operations were performed with local anesthesia

14 Powers, J H Vital Capacity Its Significance in Relation to Postoperative Pulmonary Complications, *Arch Surg* **17** 304 (Aug) 1928

15 Blumgart, H L, Gargill, S L, and Gilligan, D R Studies on the Velocity of the Blood Flow, *J Clin Investigation* **9** 91, 1930

per cent (from 22 to 41 per cent) of the calculated normal Peabody<sup>6</sup> demonstrated that persons with a vital capacity below 45 per cent are in a state of frank decompensation. The remaining 9 patients (64 per cent) had a vital capacity between 45 and 64 per cent and were severely handicapped. A later determination of vital capacity was made just before the operation, following a period of rest in bed and digitalization. Such medical treatment resulted in an average increase in vital capacity of 9 per cent, an average rise from 43.3 to 52.2 per cent in 11 of the 14 cases, the vital capacity in the remaining 3 showing no change. Total thyroidectomy was followed by an immediate decrease in vital capacity in 43 per cent of the cases, that in the other 57 per cent maintaining the preoperative level or showing a slight increase. There was an increase in vital capacity averaging 15 per cent in 9 of the patients in the myxedematous state as compared to the immediate preoperative level, or a total increase of 24 per cent (9 per cent following preoperative medical treatment plus 15 per cent following total thyroidectomy). The remaining 5 patients showed no appreciable change after myxedema was established as compared to the immediate preoperative vital capacity. In all the cases, however, there was a marked general symptomatic improvement, although the highest vital capacity was only 71.9 per cent of the calculated normal. Peabody<sup>6</sup> stated that patients with cardiac disturbances with a vital capacity of from 40 to 70 per cent of normal are severely handicapped. The degree of incapacity appears to be less marked in previously decompensated patients following total thyroidectomy than in a similar group of decompensated patients who have not been subjected to total thyroidectomy. In summary, although the vital capacity did not attain the level of activity (70 per cent, as given by Peabody), all the patients improved sufficiently to become ambulatory after the operation, whereas they were all bedfast before the removal of the gland.

#### VOLUME OF BLOOD FLOW

Studies in the volume of blood flow in normal persons as well as in persons with cardiac disease have been carefully made by Blumgart and Weiss<sup>16</sup>. They concluded that in persons with cardiovascular disease there is a striking tendency for a decrease in the vital capacity of the lungs to be associated with an increase in the pulmonary circulation time, which denotes a slower rate of blood flow through the lungs. Our observations are in agreement. Our technic differed in that in place of making an active deposit of radium, as done by Blumgart and Weiss,

<sup>16</sup> Blumgart, H. L., and Weiss, S. Clinical Studies on Velocity of Blood Flow, *J. Clin. Investigation* 5: 343 and 379, 1928.

we gave an intravenous injection of 2 per cent sodium cyanide<sup>17</sup> This method measures the arm to carotid artery circulation time, the principle being essentially the same Blumgart and his associates<sup>15</sup> maintained that the arm to heart circulation time shows considerable variation because of relatively great spontaneous fluctuations in the blood flow in the arm However, our results were sufficiently accurate to warrant the use of the method in this study

The circulation time in the patients with angina pectoris, who in the absence of cardiac failure were considered essentially normal, with an average rate of twenty and one-tenth seconds, was slightly higher than the standard (fifteen and six-tenths seconds) given by Robb and Weiss Within one week after total thyroidectomy the same patients showed essentially no change, with an average of twenty and six-tenths seconds Considering, for example, that a doubling of the circulation time denotes a slowing of the blood flow to one-half its normal velocity and designating it as — 50 per cent, we observed that as the same patients became myxedematous the circulation time increased to an average of thirty-three and four-tenths seconds, a slowing of the blood flow of — 43 per cent in 13 cases (81 per cent) In 3 cases (19 per cent) there was no appreciable change after myxedema was established as compared to the preoperative velocity The discrepancy may be explained in 1 case by the fact that a high basal metabolic rate persisted, though there was clinical evidence of myxedema The basal metabolic rate was +3, with the cholesterol content of the blood 610 mg per hundred cubic centimeters In the other two cases, however, the basal metabolic rate was —23 and —24 We are unable to explain this phenomenon In general, we noted, as pointed out by Blumgart and his associates,<sup>15</sup> that the relation between the basal metabolic rate and the velocity of the blood flow is a simple linear one, although it cannot be expressed on a mathematical basis, as the basal metabolism falls, the blood flow slows proportionately Following the administration of thyroid substance the basal metabolic rate rose and the velocity of the blood flow increased toward normal in a parallel manner (chart 2)

In the study of the group with cardiac failure the changes noted were not nearly so clear and striking We noted that while in general the velocity of the blood flow was retarded it could not be related closely to clinical observations in regard to either the original cardiac failure or the later myxedema The average preoperative circulation

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17 Robb, G P, and Weiss, S A Method for Measurement of the Velocity of Pulmonary and Peripheral Venous Blood Flow in Man, *Am Heart J* 8 650, 1933

rate in 13 patients was thirty-four and eight-tenths seconds, a distinct slowing compared to the rate of normal persons (twenty seconds in the group with angina pectoris and fifteen and six-tenths seconds observed by Robb and Weiss) Within one week after total thyroidectomy the average velocity in the same patients was thirty-two and five-tenths seconds, an apparently small variation from the previous determination. Actually, 63.6 per cent of the patients showed an increased velocity of the blood flow after the operation whereas the remaining 36.4 per cent showed a greater slowing of the circulation. In patients in the myxedematous state, the same individual variation existed as compared to the postoperative velocity, although in all cases there was a striking slowing of the velocity of the blood flow (from

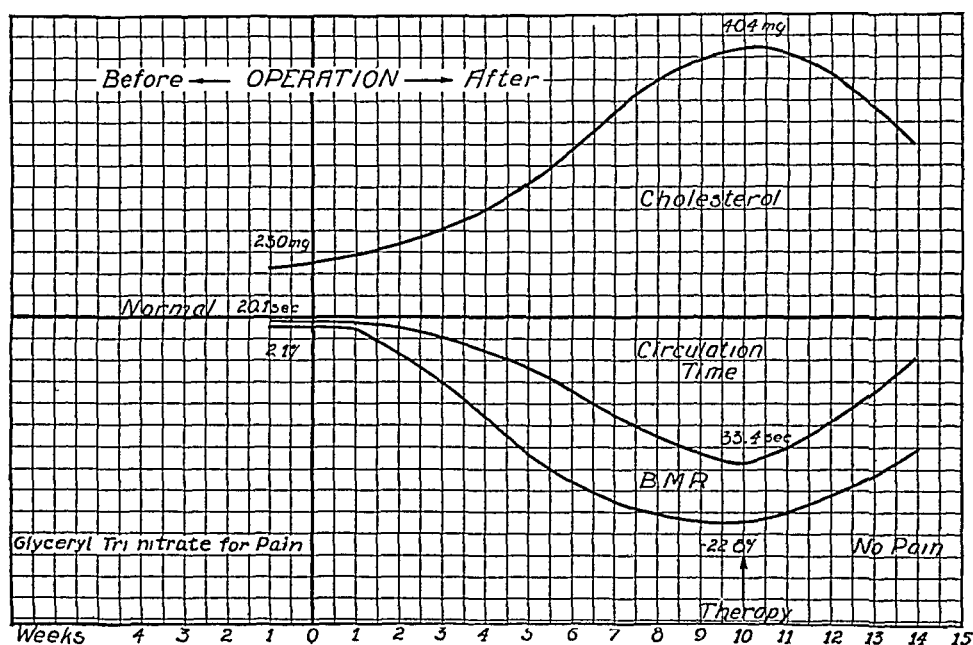


Chart 2—Ratio of the metabolic rate to the circulation time and the cholesterol content of the blood before and after operation for removal of the thyroid gland and after thyroid therapy in twenty-two patients with angina pectoris

thirty to ninety seconds) This is undoubtedly the slowed velocity associated with the myxedema superseding the increased velocity usually observed in persons with cardiac compensation. This was confirmed by giving small doses of thyroid extract by mouth, which caused an increase in the velocity of the blood flow, only to be superseded by a fall again if decompensation ensued. In 1 case in which there was marked decompensation due to mitral stenosis and insufficiency, the slow blood flow became more rapid after total thyroidectomy. This we interpreted as being due to the fact that the slow rate of flow due to hypothyroidism was not at as low a level as the slower rate dictated



by the cardiac decompensation. Thus, total thyroidectomy can increase the volume of blood flow when it has been abnormally slowed during cardiac failure, although one of the intrinsic results of total thyroidectomy is to slow the volume of blood flow.

#### OTHER CHEMICAL ANALYSES OF THE BLOOD

In view of the fact that total thyroidectomy with the removal of a normal gland is a decidedly new procedure in man, additional chemical analyses of the blood were carried out in order to observe any further changes that might occur following such a procedure. It is true that such studies have been carried out on laboratory animals many times, but the results have been controversial. In this study no attempt was made at dietary control, the patients receiving the average full hospital diet before the operation and as soon after the operation as solid food could be taken without discomfort. This was usually by the second or third postoperative day, so that all the studies were made with the patient on an average diet. All the specimens of blood were taken after fasting.

*Calcium and Phosphorus*—The calcium<sup>18</sup> and the phosphorus<sup>19</sup> content of the blood serum were determined in 25 patients (both groups included) before the operation and at intervals after the operation. Preoperatively and postoperatively, as well as during myxedema and after thyroid therapy, there was a fluctuation of values for both the calcium and the phosphorus content of the blood, but all were within normal limits (calcium, from 9 to 11 mg and phosphorus from 3.4 to 4.6 mg per hundred cc of blood<sup>20</sup>). Eppinger and Hess<sup>21</sup> and Maxim and Vasilin<sup>21</sup> noted that the calcium content of the blood in dogs increased after thyroidectomy. Waldorf and Fuller,<sup>21</sup> as well as Larson and Fisher,<sup>21</sup> maintained that thyroidectomy decreases the calcium content of the blood. Our observations agree with those of Ido<sup>21</sup> that the calcium content fluctuates considerably but remains essentially within normal limits. This is of particular interest in view of the fact that in the first 26 cases parathyroid tissue was observed either grossly or microscopically in 50 per cent of the thyroid glands examined.

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18 Fiske, C. H., and Logan, M. A. Determination of Calcium by Alkalimetric Titration, *J Biol Chem* **93** 211, 1931.

19 Fiske, C. H., and Subbarow, Y. The Colorimetric Determination of Phosphorus, *J Biol Chem* **66** 375, 1925.

20 Salvesen, H. A., and Linder, G. C. Inorganic Bases and Phosphates in Relation to Protein of Blood and Other Body Fluids in Bright's Disease and in Heart Failure, *J Biol Chem* **58** 617, 1923.

21 Quoted by Koh, Munlyong. A Method of Estimating the Functional Activity of Thyroid by Means of Urine or Serum, *Keijo J Med* **4** 291, 1933.

The amount of parathyroid substance removed is not the sole consideration, as shown by the fact that tetany occurred infrequently and never in a severe form. We have learned to consider of less serious import the possibility of tetany following the removal of some parathyroid tissue.

Signs of parathyroid tetany developed in two of the patients after total thyroidectomy, it was mild, with a 1+ Trousseau sign but a negative Chvostek sign. In one patient, two parathyroid glands were reimplanted into the pretracheal muscles at the time of operation, one parathyroid remaining intact, as noted later at autopsy. In the other patient, two parathyroid glands were well visualized and were left intact. Both patients showed a lowered calcium content of the blood of 6.5 and 7.8 mg per hundred cubic centimeters, respectively, at the onset of symptoms. The phosphorus content of the blood in the first case was elevated to 5.7 mg per hundred cubic centimeters and in the other case was normal, 4 mg. The first patient (S. A.) was treated with parathyroid extract, resulting in a fall of the phosphorus content to 4.1 mg on the following day but no change in the calcium content. The patient received a total of 208 units of parathyroid extract intramuscularly plus calcium gluconate intravenously in one week, with no rise in the calcium content of the blood or later alteration in the phosphorus content, although the symptoms subsided. The other patient (A. P.) received large doses of calcium lactate (4 Gm three times a day) and viosterol, 20 drops three times a day by mouth, with a rapid rise of the calcium content to 9 mg per hundred cubic centimeters and relief from the symptoms. There was a slight elevation in the phosphorus level during treatment (from 4 to 5.4 mg), not related to his symptoms. In the patient A. P. simultaneous studies of the protein contents of the blood were carried out, and the values were observed to be normal (total protein, 7.2 Gm, albumin, 4.3 Gm, and globulin, 2.9 Gm). Salvesen and Linder,<sup>22</sup> in a study of parathyroidectomy in dogs in which tetany subsequently developed, observed that the protein content of the plasma remained normal while the calcium content of the serum decreased. They concluded that this is an indication that the decrease of calcium in cases of tetany is not due to a primary decrease in the protein-bound calcium but is caused by a decrease in the diffusible and ionized fraction. Furthermore, it appears probable that a parallel fall in both the protein and the calcium content of the plasma, with  $p_H$  and other significant factors normal, affects chiefly the nonionized calcium, while a fall in the calcium content with

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22 Salvesen, H. A., and Linder, G. C. Relation Between Calcium and Protein of Serum in Tetany Due to Parathyroidectomy, *J Biol Chem* **58** 635, 1923

a continued normal protein content affects chiefly the ionized calcium and leads to tetany

*Protein*—Studies of the protein content of the blood,<sup>23</sup> including determinations of total protein, albumin and globulin, were carried out on a series of patients before operation, again when myxedema was established and after thyroid therapy. They showed some fluctuations, which were not constant in any phase of the study and were all within normal limits, so that the further study was abandoned. Rossignoli and his co-workers<sup>24</sup> in studies of the blood of dogs observed that following total thyroidectomy there was a rise of the total protein and the nonprotein nitrogen content of the blood to the upper limits of normal. The values returned to the normal average after the administration of thyroid substance. Our studies revealed a tendency toward lowering of the total protein content of the blood in patients with myxedema to a lower limit of normal with no appreciable change in the values for nonprotein nitrogen. Thyroid therapy did not raise the total protein content in these cases.

*Potassium*—Studies<sup>25</sup> were carried out, since Maxim and Vasilin<sup>21</sup> stated that the potassium content begins to decrease from four to seven days after thyroidectomy in dogs. Ido<sup>21</sup> reported an increase in the potassium content of the blood of thyroidectomized guinea-pigs. With the normal limits for potassium from 18 to 22 mg per hundred cubic centimeters,<sup>26</sup> we observed a great variation in the potassium content, from 17.5 to 26.3 mg in the group with angina pectoris and from 17 to 36.8 mg in the group with cardiac failure, irrespective of the patient's clinical condition in relation to thyroid function. Salvesen and Linder<sup>20</sup> also observed that the values for potassium varied in both directions but were relatively constant in patients with cardiac failure. Hoffman and Jacobs,<sup>27</sup> in their study of the potassium content of the blood in health and in disease, observed no variation from the normal either in persons with hyperthyroidism or in those with hypothyroidism.

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23 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 693.

24 Rossignoli, J. J., di Benedetto, E., Guerrero, I., and di Benedetto, E. J. *Modifications physico-chimique du sang des chiens ethyroïdes*. *Compt rend Soc de biol* **113** 450, 1933.

25 Sobel, A. E., and Kramer, B. A New Colorimetric Method for Potassium, *J Biol Chem* **100** 561, 1933.

26 Kramer, B., and Tisdall, F. F. The Distribution of Sodium Potassium, Calcium, and Magnesium Between Corpuscles and Serum of Human Blood, *J Biol Chem* **53** 241, 1922.

27 Hoffman, W. S., and Jacobs, H. R. Partition of Potassium Between Serum and Corpuscles in Health and Disease, *J Lab & Clin Med* **19** 633, 1934.

*Iodine*—Study of the iodine content of the blood of man<sup>28</sup> and the interpretation<sup>29</sup> of results are comparatively recent and are becoming of universal interest. The method of determination of the iodine content most commonly used is that of von Fellenberg,<sup>30</sup> this is an open reduction method yielding an average iodine content of 12.8 micrograms per hundred cubic centimeters of blood in the late summer and fall and 8.3 micrograms during the late fall and winter in Munich, Germany. Curtis,<sup>29</sup> in this country, using the same method, reported the range of iodine values from 8.9 to 13.8 micrograms, with an average of 12 micrograms per hundred cubic centimeters of blood in Chicago. He likewise reported a range of from 5.2 to 14.2 micrograms, with an average of 10.1 micrograms per hundred cubic centimeters of blood in Columbus, O. Although these figures are relatively constant, we are of the opinion that they probably represent a nonvolatile fraction of iodine in the blood, an unknown fraction having been volatilized in the open method of reduction. We therefore utilized the closed reduction method of Baumann and Metzger<sup>31</sup> for the determination of iodine in the blood of patients subjected to total thyroidectomy for cardiac disease.<sup>32</sup> In the vicinity of Boston between Dec 1, 1933, and June 1, 1934, we noted a wide variation in values for iodine in the blood of persons without thyroid disease. In 7 patients with angina pectoris the iodine content after fasting before operation ranged from 20 to 380 micrograms per hundred cubic centimeters of blood. This became elevated to a range of from 28 to 660 micrograms per hundred cubic centimeters of blood six days after the operation. In persons with myxedema the values ranged from 40 to 220 micrograms. This last range was very little altered by the administration of small amounts of thyroid substance. Similar results were obtained in 9 patients in the group with cardiac failure, the preoperative range being from 10 to 200 micrograms per hundred cubic centimeters of blood. There was no relationship between the values for iodine and the severity of the cardiac disturbance. The patients did not receive iodine in the form of medication or iodized salt except thyroid substance after myxedema developed.

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28 Davis, B., Curtis, G. M., and Cole, V. Blood Iodine Studies. Normal Iodine Content of Human Blood, *J Lab & Clin Med* **19** 818, 1934.

29 Curtis, G. M., Davis, C. B., and Phillips, F. J. Significance of Iodine Content of Human Blood, *J A M A* **101** 901 (Sept 16) 1933.

30 von Fellenberg, T. Das Vorkommen der Kreislauf und der Stoffwechsel des Jods, *Ergebn d Physiol* **25** 176, 1926.

31 Baumann, E. J., and Metzger, N. Determination of Iodine in Blood, Foods, and Urine, *J Biol Chem* **98** 405, 1932.

32 Mr H. W. Cumings carried out the work and is making a full report on the studies of the iodine content of the blood in a later communication.

Two patients with heart disease recently observed were selected for study of the iodine content immediately after thyroidectomy. One patient (M A), a woman with cardiac failure and a basal metabolic rate of  $-1$  per cent had one week after menstruating an iodine content of 10 micrograms per hundred cubic centimeters of blood. The other patient (H B), a man with angina pectoris (decubitus), had a basal metabolic rate of  $-5$  and an iodine content of 60 micrograms per hundred cubic centimeters of blood. Two preliminary determinations of iodine were made on each patient, the second sample being taken the morning of operation. All samples were taken after fasting. Subsequent samples of blood were taken twelve and twenty-four hours following operation and for each twenty-four hour period thereafter for one week. The iodine level began to rise after total thyroidectomy, reaching its peak in one hundred and forty-four hours (six days) in the patient M A, and in seventy-two hours (three days) in the patient H B. We do not believe that this represented a liberation of thyroid substance into the blood stream at the time of removal of the gland, since the content cumulated over a period of several days. The iodine content of the urine was not determined. The basal metabolic rates for the 2 patients one week after operation were  $-8$  and  $-5$ , respectively.

Chart 3 shows the level of iodine in the blood at each twenty-four hour period.

The rise in the iodine content of the blood following total thyroidectomy, with a decline toward the normal preoperative level in one week, was not the same as that observed by Curtis,<sup>33</sup> who noted a transient increase in the iodine content after total thyroidectomy which subsided after twenty-four hours. We are unable to explain the continued rise along with the great variation in the content. Schittenhelm and Eisler<sup>34</sup> expressed the opinion that there are several depots of production of iodine in the body, namely, the thyroid gland ("endocrine iodine") and certain tissues, especially voluntary muscle ("fixed tissue iodine"). They further proposed that both the production and the consumption of iodine in the blood are controlled by the central nervous system (hypophysis) and that the height of the level of iodine is an expression of a combined action of production, consumption and the activity of the nervous system. As for the thyroid gland, it is a focus of production of endocrine iodine and therefore only a factor in tissue activity.

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33 Curtis, G M, and Barron, L E. Blood Iodine After Total Thyroidectomy in Man, *Am J Physiol* **109** 26, 1934.

34 Schittenhelm, A and Eisler, B. Blutjodspiegel und dessen Beeinflussung durch sympathicomimetische Pharmaca in ihrer Abhängigkeit von Nervensystem und Schilddrüse, *Ztschr f d ges exper Med* **86** 309, 1933.

Although the authors' work is not conclusive, it offers a partial explanation for the variation occurring in our patients, considering our method of chemical analysis as being accurate

*Sugar*—As early as 1904 Lorand<sup>35</sup> demonstrated the disappearance of diabetes in three depancreatized dogs ten days after thyroidectomy. In 1908 Eppinger, Falta and Rudinger<sup>36</sup> and in 1909 MacCallum<sup>37</sup> repeated the study and obtained a diminution but not a complete disappearance of glycosuria. Crile,<sup>38</sup> in a study of 620 cases of hyperglycemia with or without glycosuria, observed that in 420 the condition cleared up completely after subtotal thyroidectomy. In the remaining 200 cases a frankly diabetic condition was present. Of these, thyroidectomy was followed by improvement in 55 per cent, in 15 per cent the

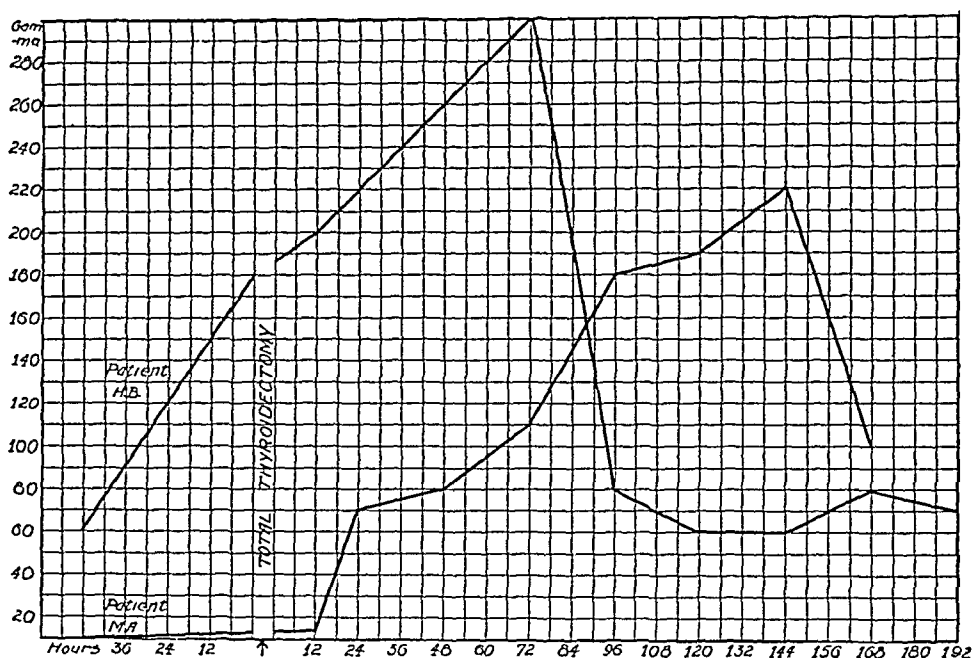


Chart 3—The iodine content of the blood following total thyroidectomy in two patients

condition remained stationary, and in 30 per cent it became more severe. Wilder and his associates<sup>39</sup> reported a case of diabetes in which total

35 Lorand, M. A. Les rapports du pancreas (îlots de Langerhans) avec la thyroïde, *Compt rend Soc de biol* **1** 488, 1904

36 Eppinger, H., Falta, W., and Rudinger, K. Ueber die Wechselwirkungen der Drüsen mit innerer Sekretion, *Ztschr f klin Med* **66** 1, 1908

37 MacCallum, W. G. On the Relation of Islands of Langerhans to Glycosuria, *Bull Johns Hopkins Hosp* **20** 265, 1909

38 Crile, G. W., and others. *Diagnosis and Treatment of Diseases of Thyroid Gland*, edited by Amy F. Rowland, Philadelphia, W. B. Saunders Company, 1932

39 Wilder, R. M., Foster, R. F., and Pemberton, J. de J. Total Thyroidectomy in Diabetes Mellitus, *Endocrinology* **18** 455, 1934

thyroidectomy caused an increased tolerance for sugar (lower sugar curve) but did not cure the condition

Our study includes observations on 12 nondiabetic persons on whom total thyroidectomy was performed for relief from cardiac disease. Tests for sugar tolerance were considered before operation and at subsequent intervals. Although several patients showed a high normal curve, there were neither symptoms of diabetes nor glycosuria. We noted that following total thyroidectomy, with the removal of a normal gland in nondiabetic persons, there was a tendency to lowering of the curve in a few instances, but in no case was it sufficiently great to be of any significance, even with fairly severe myxedema. Table 1 shows the tolerance curves for 6 patients, 3 with angina pectoris and 3 with congestive heart failure, before operation and with hypothyroidism.

TABLE 1—*Sugar Tolerance of Six Patients Before and After Total Thyroidectomy*

Patient	Diagnosis	Time of Study	B M R Percentage Deviation from Normal	Blood Sugar, Mg per 100 Cc				
				After Fasting	After Administration of 100 Gm Dextrose			
					½ Hr	1 Hr	1½ Hr	2 Hr
A W	Angina pectoris	Preoperative	— 9	133	178	242		242
		Postoperative	— 5	134	194	233	233	232
		During myxedema	—28	82	148	198	204	185
C W	Angina pectoris	Preoperative	—13	76	142	148	154	121
		Postoperative	—21	91	163	133	129	120
		During myxedema	—32	79	108	155	153	152
R H	Angina pectoris	Preoperative	—12	100	150	156	160	180
		Postoperative	—10	91	126	160	200	152
		During myxedema	—33	68	89	133	122	101
C C	Cardiac failure	Preoperative	+ 2	134	168	235		208
		Postoperative	—15	78	142	154	216	185
		During myxedema	—31	81	118	150	170	175
E F	Cardiac failure	Preoperative	— 6	87	135	198	161	187
		Postoperative	— 8	115	129	148	194	208
		During myxedema	—22	79	152	200	224	247
A P	Cardiac failure	Preoperative	— 1	84	150	202	219	210
		Postoperative	— 2	83	147	194	217	215
		During myxedema	—36	88	123	155	178	177

Two patients with mild diabetes mellitus having early gangrene of the foot were selected for total thyroidectomy with the thought of saving the damaged extremity. The physiologic reasons were as follows: Total thyroidectomy should reduce the intimate basal metabolic demands in all the tissues of the body, affecting even individual cells. It is possible that under such circumstances the cells which could not live with the damaged circulation plus the diabetes found that under the condition of the decreased metabolic demands the previously inadequate circulation became adequate. The operation was successful in that in both cases the diseased extremity healed without local operation. The good result obtained may in part have been due to the diminished metabolic demands of the tissue and to the vasodilator effect produced by the thyroidectomy on the blood vessels through the sympathetic nervous

system and adrenal glands<sup>40</sup> The diabetic condition was distinctly benefited Both patients are now ambulatory, 1 (D M) having required no insulin for the past six months and the other (G K) now using 5, 0 and 5 units daily Both used 10, 0 and 10 units daily, before thyroidectomy Table 2 shows the tolerance for sugar in relation to thyroid metabolism for the two subjects

It appears that in patients having no disturbance in sugar metabolism total removal of the thyroid gland does not alter the tolerance for sugar appreciably, whereas in patients having diminished tolerance for sugar (diabetes mellitus) total thyroidectomy increases the tolerance for sugar as early as one week after the gland has been removed and before a frank state of myxedema develops Feeding of thyroid substance with a return of the basal metabolic rate toward normal does not

TABLE 2—*Sugar Tolerance Curves of Two Diabetic Patients Before and After Total Thyroidectomy*

Patient	Date		Blood Sugar, Mg per 100 Cc					Basal Meta bolic Rate
			After Fasting	After Administration of 100 Gm Dextrose				
				½ Hr	1 Hr	1½ Hr	2 Hr	
G K	10/ 5/33	Preoperative	212	242	308		361	— 7
	10/18/33	Postoperative	169	176	204		267	—13
	1/ 6/34	During myxedema	146	194	266	274	270	—27
	4/18/34	After thyroid therapy	163	206	227	244	225	— 3
	1/18/33*	After thyroid therapy	93	129	140	169	210	—20
D M	10/20/33	Preoperative	132	156	184	238	290	—14
	11/10/33	Postoperative	99	129	155	210	222	— 8
	2/ 1/34	During myxedema	146	225	282	307	294	—16
	4/17/34	After thyroid therapy	136	141		202	190	— 4
	12/17/34†	After thyroid therapy	133	156	224	278	200	—18

\* Present medication is thyroid, 0.015 Gm daily, insulin, 5, 0 and 5 units daily, and digitals, 0.1 Gm daily

† Present medication is thyroid extract, 0.030 Gm daily No insulin has been required for six months

alter the improved tolerance appreciably The normal persons may perhaps show a similar change in tolerance for sugar after a more prolonged period in the myxedematous state

#### STUDIES OF THE TEMPERATURE OF THE SKIN

In our study of patients subjected to total thyroidectomy, determinations of the temperature of the skin were made before and after operation to study further the relationship between the thyroid gland and the vasomotor apparatus Lewis and Pickering<sup>41</sup> stated that while

40 Cutler, E C, and Schnitker, M T Skin Temperature Changes After Total Thyroidectomy, *Proc Soc Exper Biol & Med* **31** 736, 1934

41 Lewis, T, and Pickering, G W Vasodilatation in Limbs in Response to Warming the Body, with Evidence for Sympathetic Vasodilator Nerves in Man, *Heart* **16** 33, 1931



the vessels of the skin are directly affected by temperature, constricting with cold and dilating with heat, they are also affected through the sympathetic nerves by the temperature to which distant areas of the body are exposed. That the vasoconstrictor tone of the capillaries is a function of the sympathetic nervous system was pointed out years ago by Krogh. The medulla of the adrenal gland is believed to reenforce the activity of the sympathetic nervous system, especially during conditions of stress<sup>42</sup>. Moreover, the thyroid gland appears to sensitize the whole or part of the sympathetic nervous system<sup>43</sup>. Because of the close interrelationship of the thyroid, the adrenals and the vessels of the skin through the sympathetic nervous system, we endeavored to study the relationship more closely by means of studies of the temperature of the skin in relation to ablation of the thyroid.

Lewis and Pickering<sup>41</sup> noted that the temperature of the skin is a resultant of two factors: (1) the state of dilatation of the smaller vessels (arterioles and capillaries) and (2) the amount of blood flowing through the part. Pickering<sup>44</sup> further demonstrated that the application of cold to the skin reflexly produces over the entire body a vasoconstriction which is transient and quickly abolished by warming the skin. The application of heat to the skin does not produce vasodilatation reflexly, but the rise in the temperature of the skin over the entire body is due to the stimulation of some central mechanism by the warm blood transported from the heated part. As the body slowly warms, the sympathetic tone of the smaller vessels decreases, the vessels relax and the temperature of the tissues rises; this rise of temperature, acting locally, further dilates the vessels, so that the temperature of the skin rises to its maximum, depending on the combined activity of the central and peripheral mechanisms.

The methods now used to establish vasomotor relaxation are the injection of foreign proteins to produce fever, general and spinal anesthesia and local and sympathetic nerve block to restricted areas. The resulting responses are manifested by changes in the temperature of the skin, which are easily measured by a thermocouple, such as the Tycos dermatherm<sup>45</sup>. With this instrument the changes are measured directly on the millivoltmeter and are easily calculated from a constant known temperature of water in a thermos bottle. To produce vasomotor

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42 Cannon, W. B. The Emergency Function of the Adrenal Medulla in Pain and the Major Emotions, *Am J Physiol* **33** 356 1914

43 Wright, S. *Applied Physiology*, New York, Oxford University Press, 1929, p. 130

44 Pickering, G. W. The Vasomotor Regulation of Heat Loss from the Human Skin in Relation to External Temperature, *Heart* **16** 115, 1932

45 Scott, W. J. M. An Improved Electrothermal Instrument for Measuring Surface Temperature, *J. A. M. A.* **94** 1987 (June 21) 1930

relaxation we adopted the technic of Gibbon and Landis<sup>46</sup> of immersion in a hot water bath because of its simplicity in execution, consistency in results and apparent effectiveness in relaxing vasomotor tone, supposedly equal to those of the usual methods using general or spinal anesthesia. The method consists in placing the forearms of the patient in warm water at 43 C (110 F) and during the period of immersion of recording the temperature of the skin at the knee, ankle and great and small toes of each extremity at one minute intervals. The water is kept at a constant temperature by two electric thermostats, and the arms are kept in the water for thirty minutes or longer, until complete vasodilatation has been accomplished.

The patient is first made comfortable in bed in a modified Fowler position in a room at from 68 to 72 F and free from air currents. The patient's arms and legs are exposed for at least fifteen minutes to become adjusted to the temperature of the room, and then the temperature of the skin is noted over a period of another fifteen minutes to obtain a base-line before the forearms are immersed in water. Immediately on immersion of the forearms there is an initial drop in skin temperature, averaging from 0.5 to 1 C, that is a result of reflex vasoconstriction due to the sudden excess stimulus<sup>47</sup>. After a period of from two to five minutes the skin temperature returns to the original level and then slowly rises to about the fifteen minute interval, after which it rises more rapidly to the maximum level. During the period of rise of temperature, the patient perspires freely but is not unduly uncomfortable. The body temperature rises on an average of from 0.4 to 0.6 F (rectal).

According to Morton and Scott,<sup>48</sup> there is a maximum vasodilatation response for normal vessels that they have designated the normal vasodilatation level. The lower limit of the maximum level for the surface temperature of the great toe, the vasoconstrictors of which have been released by general or spinal anesthesia, is 31.5 C (88.7 F) at a room temperature of 20 C (69 F). For the vessels that are not able to reach this level Morton and Scott have set up an arbitrary

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46 Gibbon, J. H., Jr., and Landis, E. M. Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, *J. Clin. Investigation* **11** 1019, 1932. Landis, E. M., and Gibbon, J. H., Jr. A Simple Method of Producing Vasodilatation in Lower Extremities with Reference to Its Usefulness in Studies of Peripheral Vascular Disease, *Arch. Int. Med.* **52** 785 (Nov.) 1933.

47 (a) Bazett, H. C. Physiological Responses to Heat, *Physiol. Rev.* **7** 531, 1927. (b) Martin, E. G., and Jacoby, L. A. Vasoconstriction from Warmth Stimulation, *Am. J. Physiol.* **59** 394, 1922.

48 Morton, J. J., and Scott, W. J. M. Methods for Estimating the Degree of Sympathetic Vasoconstriction in Peripheral Vascular Disease, *New England J. Med.* **204** 955, 1931.

standard called the occlusion index. The index is determined by subtracting the highest temperature attainable in the area of a diseased vessel from 31.5 C, and this figure is the index of the amount of circulatory occlusion. We noted in using the technic of Gibbon and Landis for vasodilatation that the standard of 31.5 C is too high with this method, the normal vasodilator ability in our series of cases averaging 30.5 C.

In instances of variation of room temperature above or below 20 C, we applied Vincent's formula,<sup>48</sup> since it appeared that a correction factor was necessary in order to place all determinations of skin temperature on a common basis as regards environmental conditions, especially on hot days. Vincent's formula corrects the environmental factor by subtracting 0.3 C from the skin temperature for each degree of room temperature above 20 C and adding 0.3 C to the skin temperature for each degree below 20 C of room temperature. This has been accepted by Morton and Scott<sup>48</sup> but not by Cobet,<sup>49</sup> who expressed the opinion that its general application could not be used because of Vincent's technic.

It is interesting to note that in recording the skin temperature at the knees and toes we observed the knees showed the first and most rapid rise, the temperature of the toes rose more slowly at first but later far exceeded the rise at the knees. This conformed directly to the so-called vasoconstrictor gradient,<sup>47b</sup> which means that the distal parts of the body are cooler than the central part because vasoconstriction progresses from the body outward to the extremities.

Studies of skin temperature were made on a series of 24 patients before operation, and the vasodilator response was determined. A total thyroidectomy was then carried out with local anesthesia, thereby making it possible to carry out postoperative studies. When a general anesthesia has been used, the results of postoperative studies are too variable and are not reliable, since the anesthesia gives complete vasomotor relaxation.<sup>50</sup> To determine what effect the operation per se with local anesthesia might have on the temperature of the skin a series of 6 patients having various conditions requiring medical and surgical treatment not related to the thyroid gland or circulatory apparatus were used as controls. These control studies showed such slight variations within normal limits that we were able to conclude that rest in bed, an operation with local anesthesia or a repetition

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49 Cobet, R. Die Hauttemperatur des Menschen, *Ergebn d Physiol* **25** 439, 1925.

50 Herrick, J. F., Essex, H. E., and Boldes, E. J. Effect of Lumbar Sympathectomy and Flow of Blood in Femoral Artery of Dog, *Am J Physiol* **101** 213, 1932.

of the test did not give rise to the vasomotor changes which we observed following total thyroidectomy

In the same 24 thyroidectomized patients, studies were carried out on the fourth postoperative day, again when clinical myxedema was established and later after the administration of thyroid substance

We observed that immediately after operation, while the patient still maintained the normal basal metabolic rate, there was a tendency to a higher initial temperature of the skin than before operation, the increase being an average of 1 C in both the group with angina pectoris and the group with cardiac failure. Very interesting is the fact that throughout all the phases of study the average skin temperature of the patients with cardiac failure as a group was from 1 to 2 C higher than that of the group with angina pectoris. As regards the vasodilator ability, both groups showed an average rise to 31.5 C, a rise of 1 degree higher than the preoperative vasodilator level. We believe these changes to be due to a diminished vasomotor tone, with a relaxation of the smaller vessels (arterioles and capillaries), thereby permitting a greater volume of blood flow through the vessels.

When the patient reached the state of myxedema we observed, as have Talbot<sup>51</sup> and Maddock and Coller,<sup>52</sup> that the initial temperature of the skin was lower than in the normal state. However, we noted that the vessels of their skin were capable of dilatation equal to the preoperative level in most instances, although it required a little longer time to reach that level. The delay was probably due to the myxedematous infiltration into the skin and to the slowing of the circulation. Perspiration was less at this time also.

The feeding of thyroid substance to these patients tended to raise the initial temperature of the skin as well as the vasodilator response, although this reaction varied considerably in different persons, since they responded inconsistently to thyroid substance. The group with cardiac failure showed their best vasodilator ability after the administration of thyroid substance, although they were given only small amounts of thyroid substance to maintain an optimum state, near myxedema. In 2 patients with valvular heart disease the basal metabolism was brought back to a normal level with the administration of thyroid substance, both showed greatly improved peripheral circulation, having an initial temperature of 30.9 and 31.5 C, with a vasodilator ability to 31.9 and 32 C, respectively. The initial temperature preoperatively (during failure) was 29.8 and 26 C, respectively.

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<sup>51</sup> Talbot, F. B. Skin Temperature of Children, *Am J Dis Child* **42** 965 (Oct) 1931

<sup>52</sup> Maddock, W. G., and Coller, F. A. The Rôle of the Extremities in the Dissipation of Heat, *Am J Physiol* **106** 589, 1933

The results seem to indicate a definite link between the thyroid gland and the vasomotor apparatus. They definitely suggest a diminished sympatheticotonic-adrenal activity following total thyroidectomy<sup>40</sup>. It would appear that the vasodilator response in patients from whom the thyroid gland has been removed in toto might suggest some utilization of the observation in the future treatment of patients with peripheral vascular disease.

#### MENTAL TESTS

Simple mental tests (suggested to us by Dr F L Wells) have been carried out to determine the variation of the more simple sensory and motor functions in patients with myxedema as compared to the preoperative normal level for each patient. The examination is made up of symbol-formation tests in three parallel series, devised to enable repetition of the examination at varying intervals without duplication. Each series consists of eleven tests of such simple nature as to be a measure of reaction time rather than of intellect, except the test of addition. The symbols are placed on small cards and the time recorded, measured in seconds, required to name the symbols.

1 The first test consists of naming twenty actual objects, such as a comb, a string, a knife and other simple household articles.

2 For naming colors there are forty colored disks, 6 mm in diameter, of red, green, blue and orange.

3 For naming digits there is a set of forty single numbers, from 1 to 9, arranged in double space on a card.

4 and 5 Naming letters requires rearrangement of all letters of the alphabet, repeated, a total of 52 (lower case—small letters, upper case—capital letters).

6 For naming pictured objects there are ten pictures, of simple subjects, such as a cow, a clock and a fish.

7, 8 and 9 These three tests are for reading the words of actual colors, objects and pictures named previously.

10 The addition test requires the addition of two figures, such as  $16 + 6$  or  $23 + 5$ .

11 The Healy test<sup>53</sup> is a block of 150 spaces, in each square of which the patient places a dot with a pencil.

As a basis for comparison of reaction time, each test of the series is compared with itself at the various intervals during observation. It appears that the person of average intelligence and dexterity can perform the usual daily functions quite as well in the state of post-operative myxedema as before operation. In fact, the changes measured by the mental test in the majority of cases showed a fairly definite increase in mental functioning in the state of myxedema (table 3).

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<sup>53</sup> This test, no 19,235, is made by C H Stoelting Company, Chicago.

Goldman<sup>54</sup> made a similar observation on another group of patients who underwent total thyroidectomy. In a further study of personality Goldman observed that the patients felt somewhat more sensitive, shy and lonely and were more prone to worry than they were prior to thyroidectomy. This increase in mental functioning was distinctly contrary to the observations made in cases of spontaneous myxedema<sup>55</sup> and is perhaps explained by the fact that concentration was better and the patients worked more deliberately and carefully and with fewer errors. It should also be borne in mind that the level of myxedema in our patients was probably never so low as that reached in persons with the idiopathic form and, further, that the compensation occurring in the cases of cardiac failure should influence the reactions favorably. We do not wish to predict the future mental status of the patients, however.

TABLE 3—*Comparison of Reaction Time (in Seconds) in Mental Tests Before and After Total Thyroidectomy*

Test	Group with Angina Pectoris			Group with Cardiac Failure		
	Pre-operative	During Myxedema	After Thyroid Therapy	Pre-operative	During Myxedema	After Thyroid Therapy
1 Naming actual objects	32.1	24.9	29.0	32.6	29.6	30.2
2 Naming colors	50.9	43.5	45.5	36.3	34.6	35.8
3 Naming digits	24.6	17.6	20.3	19.9	20.0	24.2
4 Naming letters (L C)	35.0	33.4	36.5	33.1	39.0	32.6
5 Naming letters (U C)	31.3	27.4	34.5	32.8	30.1	27.4
6 Naming objects in picture	16.0	18.2	16.8	17.3	12.3	13.6
7 Naming color words	21.3	19.0	28.3	21.0	30.7	22.2
8 Naming actual object words	19.6	18.4	28.3	15.6	44.5	35.8
9 Naming picture object words	7.7	5.0	18.0	6.1	18.3	19.4
10 Addition	90.6	44.6	58.0	65.6	112.0	112.6
11 Healy test (motor function)	84.9	76.0	76.3	81.1	79.7	70.4
Total	414.0	328.0	391.5	361.4	350.0	424.2

#### BODY WEIGHT

That the myxedematous state carries with it an associated increase in body weight has been long observed. In the group with angina pectoris whose preoperative weight was considered normal there was an increase of from 0.4 to 14.8 pounds (0.2 to 6.8 Kg), with an average of 6.6 pounds (3 Kg) for the group with myxedema. After the administration of thyroid substance there was a continued increase in weight averaging 1.8 pounds (0.9 Kg). This was, of course, because the patients still had some myxedema. The same change occurred in the group with cardiac failure, except that 3 patients (21 per cent) showed a loss of 4.2, 5.5 and 7.3 pounds (1.9, 2.5 and 3.3 Kg), respectively,

<sup>54</sup> Goldman, N. Personal communication to the authors.

<sup>55</sup> Hayward, E. P., and Woods, A. H. Mental Derangement in Hypothyroidism, J. A. M. A. 97:164 (July 18) 1931. Sturgis.<sup>2</sup>

in a myxedematous state (because of loss of the decompensation fluid) The remainder showed a gain of from 6.3 to 19.5 pounds (2.7 to 8.8 Kg), with an average of 7.8 pounds (3.6 Kg) Following thyroid therapy the gain in weight continued, with an average of 2 pounds (0.9 Kg) Thus, in the 39 cases, during an average period of observation of six months, there was an average gain of 9.1 pounds (4.2 Kg)

#### SPONTANEOUS AND INDUCED MYXEDEMA

Observations were made on the blood cell count, hemoglobin content, peripheral pain, muscle weakness and blood pressure

An unpublished study (by L. H. V. R.) of the 100 cases of spontaneous myxedema observed in the hospital during the past twenty years has brought to light some interesting facts for comparison with those of the present series of cases of myxedema resulting from total thyroidectomy

In 26 of the 100 cases there was some form of heart disease They were classified as follows: chronic myocarditis, 17; chronic cardiac valvular disease, 5; and angina pectoris, 4 In the face of this it seems paradoxical that total thyroidectomy is being carried out for the alleviation of just such forms of cardiac disease It is now well established that the total removal of a normal thyroid gland from a patient with cardiac failure produces a certain amount of cardiac reserve Sufficient reserve is produced to make practically every patient at least ambulatory if the basal metabolic rate is kept sufficiently low, since the reserve tends to follow in inverse ratio the basal metabolic rate When however, cardiac failure develops in a patient who already has myxedema, there are no means to produce a reserve other than the general measures of rest, administration of morphine and depletion therapy If these fail, death is prompt This has been the case in certain patients following total thyroidectomy in whom there developed cardiac failure even in the presence of a low basal metabolic rate Perhaps if there were some way to drive the basal metabolic rate down to a very low level in a few hours some of the fatalities could have been averted

While the production of cardiac reserve can be fairly readily demonstrated in patients with cardiac failure, objective evidence for the relief of angina pectoris is essentially nil If the theory is accepted that anginal pain results from insufficient oxygenation of the heart muscle, it may be said that the decreased metabolism resulting from thyroidectomy should enable the heart to manage on the oxygen it does receive It has been observed repeatedly, however, that the angina disappears from the moment the ablation of the thyroid gland is completed Moreover, we have to report our results in 1 case in which there was relief from angina pectoris A woman of 49 was admitted to the hospital

in 1921, with spontaneous myxedema. In 1931 she was again admitted, with the diagnosis of coronary thrombosis, and since that time she had definite angina pectoris requiring one or two tablets of glyceryl tri-nitrate for each attack. Total thyroidectomy was performed on April 24, 1934, and the patient subsequently has had a subsidence of symptoms. The gland removed was composed completely of fat and connective tissue confined within the capsule of the thyroid gland with a few scattered typical thyroid follicles.

Secondary anemia was also observed in 26 of the 100 cases of spontaneous myxedema. Three million, five hundred thousand red blood cells or less was arbitrarily set to define secondary anemia. The high incidence of anemia has not been duplicated in the series of cases of induced myxedema. The reason for this is not entirely clear, since no measures have been taken to combat anemia, chiefly because it has not been necessary. The average preoperative hemoglobin content in 16 cases of angina was 86 per cent, and the red blood cell count was 4,810,000. In the cases of induced myxedema the hemoglobin content was the same, and the red cell count was 4,580,000. In 11 cases of cardiac failure the preoperative hemoglobin content was 88 per cent and the red blood cell count 4,767,000, and after myxedema was established, 86 per cent and 4,292,000, respectively. It is to be borne in mind that the term myxedema as used in this paper means only the state of the patient before thyroid therapy is instituted. At this time the basal metabolism is by no means at its lowest level, and even after thyroid medication is begun the patient is in a state of myxedema. It may be that the duration of the myxedema has not been sufficiently long (the oldest living patient has survived just over twenty months since the operation) and that at a later date anemia will ensue. This seems to be the tendency, since the general average for the foregoing two groups following thyroid therapy reveals a hemoglobin content of 80 per cent and a red cell count of 4,193,000. The observations are not entirely in accord with those of Emery,<sup>56</sup> who noted that in persons with spontaneous myxedema there was no relationship between the degree of the anemia and the duration of the disease or the metabolic rate. We can confirm the second of his conclusions.

Hypertension was noted in 18 of the group with spontaneous myxedema. The average age for the entire group was 50.9 years, so the incidence of hypertension is not surprising. The average age of the group with angina pectoris was 58.7 years, and the incidence of hypertension was nearly 50 per cent. Contrary to our hopes, thyroidectomy, after an average lapse of about five months since the operation, has produced an elevation of about 10 mm of mercury in both the

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<sup>56</sup> Emery, E. S., Jr. The Blood in Myxedema, *Am J M Sc* **165** 577, 1923



systolic and the diastolic pressure, the levels being essentially the same during myxedema and after thyroid therapy. It was noted also that there was essentially no change in the pulse rate.

A diagnosis of chronic arthritis was made in 5 of the cases of spontaneous myxedema. This has not been noted in the cases of induced myxedema as yet. It may be that after a more prolonged myxedematous state arthritic changes will occur. What has troubled almost all the patients has been muscular pain, chiefly in the legs, which in some instances proved a trying problem. Aminopyrine has been effective when its use has been necessary. Baking and massage helped some patients. Squatting exercises have been the only means of relief in others. The fact that exercise relieves the pain in some patients militates against the theory that arteriosclerotic changes (suddenly increased as a result of high cholesterol values) may be to blame. Of course, there is always recourse to an increase in the dose of thyroid substance to alleviate the pain, although this may be at the expense of a return of mild anginal pain or slight decompensation, as the case may be.

It was somewhat surprising to observe 5 instances each of psychoneurosis and neurasthenia in the group with spontaneous myxedema, but subsequent to operation we have observed psychoneurotic tendencies and neurasthenia in a large proportion of the cases in the series with induced myxedema. The large majority of the patients are of a class prone to complain, but the postoperative complaint of weakness is so general that we are forced to believe that the operation is a factor.

On four of the patients with spontaneous myxedema autopsy was performed. All the ductless gland material from these patients was studied for pathologic changes. Other than the characteristic changes in the thyroid, no histopathologic change of note was observed. Similar studies have been made on the ductless glands of the patients with myxedema following total thyroidectomy who died, with similar results. As yet nothing has been observed pathologically which links the thyroid with the other ductless glands when these are studied either during hypofunction or after ablation of the thyroid.

#### SUMMARY AND CONCLUSIONS

In a series of 39 patients on whom total thyroidectomy was performed for intractable cardiac disease, special laboratory studies were made to observe the changes in the metabolism and in the blood that followed the removal of a normal thyroid gland in human subjects.

The patients were divided into three groups: those having angina pectoris (22), those with cardiac valvular disease in failure (15) and those with diabetes mellitus (2). Each patient was studied preoperatively as well as postoperatively, during myxedema and after the administration of thyroid substance.

The basal metabolic rate declined after total thyroidectomy, reaching an average of  $-22.8$  per cent in nine and nine-tenths weeks after operation in the group with angina pectoris. The decline in the group with cardiac failure occurred in eight and five-tenths weeks, with an average of  $-27$  per cent. Administration of 0.015 Gm of thyroid substance daily raised the level toward normal, usually in from three to four weeks.

The cholesterol content of the blood rose after total thyroidectomy, reaching an average level of 404 mg per hundred cubic centimeters of blood in the group with angina pectoris in the state of myxedema. The group with cardiac failure showed an average increase to 315 mg per hundred cubic centimeters of blood. The values declined following thyroid medication.

An inverse ratio exists between the fall in the basal metabolic rate and a rise in the cholesterol content of the blood following thyroidectomy, which need not be simultaneous and cannot be expressed on an absolute mathematical basis. The level of cholesterol in the blood appears to be a better index of the thyroid function than is the basal metabolism.

Total thyroidectomy was followed by a striking decrease in the vital capacity in 50 per cent of the patients with angina pectoris, the capacity returning to normal within one week. In the entire group with angina pectoris, who were otherwise normal, induced myxedema caused no appreciable change in the vital capacity. Sixty per cent of the group with cardiac failure showed an average increase of 24 per cent in vital capacity when in a myxedematous state, the remaining 40 per cent showed no appreciable change.

A slowing of the volume of blood flow to  $-43$  per cent as compared with normal flow occurred in the group with angina pectoris in a myxedematous state. The group with cardiac failure showed a similar change, but the slowed velocity in persons with decompensation masks that associated with myxedema. The administration of thyroid substance caused an increased velocity of blood flow, which was superseded by a fall if decompensation ensued.

The following results of chemical analyses of the blood were noted:

- 1 The calcium and phosphorus content fluctuated considerably but remained within normal limits. Tetany did not follow removal of the parathyroid glands in several cases. The calcium content need not be lowered below normal limits with early signs of deprivation of parathyroid substance.
- 2 The value for total protein was lowered to the lower limits of normal in cases of induced myxedema. The value was not altered by thyroid medication. The albumin-globulin ratio remained unaltered.
- 3 The potassium content varied in both directions but remained relatively constant following total thyroidectomy.
- 4 Persons with normal thyroid glands as well as those with induced myxedema

showed a great variation in the iodine content (16 patients) Immediately following total thyroidectomy there was an increase in the iodine content, the value reached a peak in from three to six days (2 patients) and then declined to normal 5 No significant changes in tolerance for sugar occurred either early or later following total thyroidectomy in 12 nondiabetic patients Two patients with mild diabetes mellitus were distinctly benefited by total thyroidectomy

It appears that total thyroidectomy has a distinct influence on patients with a deranged tolerance for sugar, tending to increase the tolerance, but has no appreciable effect on the nondiabetic patient as regards sugar metabolism

There was diminished vasomotor tone, with relaxation of the smaller blood vessels, most pronounced shortly after removal of the thyroid gland In persons with induced myxedema vasomotor relaxation was less pronounced, but with the associated diminished metabolic demands on the tissues, an inadequate circulation was found to become adequate

Patients with induced myxedema appear to show an increased mental function as compared to the preoperative mental state This is offset by the patients becoming more sensitive, shy and prone to worry The patients are thought to work with better concentration and deliberation when in a myxedematous state

The group with angina pectoris gained an average of 6.6 pounds (3 Kg), and the group with cardiac failure gained an average of 7.8 pounds (3.6 Kg) with myxedema as compared to the preoperative weight

In a separate review of 100 cases of spontaneous myxedema, cardiac disease occurred in 26 per cent In 1 patient with angina pectoris, total thyroidectomy relieved the pain

In a comparison of spontaneous and induced myxedema, it was noted that for the length of time the patients were followed up induced myxedema does not cause the degree of anemia observed in the group with spontaneous myxedema Total thyroidectomy was followed by an elevation of 10 mm of mercury in both the systolic and the diastolic blood pressure although there was no essential change in the pulse rate

Postoperative muscular pains in the legs followed total thyroidectomy, these were relieved by thyroid medication or exercise

Histologic studies of associated ductless glands of patients who died of spontaneous or induced myxedema revealed no pathologic changes which could link the other glands with thyroid hypofunction.

# EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

## IV CREATINE CONTENT OF HYPERTENSIVE HYPERTROPHIED HEARTS OF RATS FED WHOLE DRIED MEAT

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AND

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Factors affecting the creatine concentration of the ventricles of the heart have been studied in experimental animals<sup>1</sup> and in human subjects<sup>2</sup>. The present investigation was undertaken to study the deposition and concentration of creatine in the cardiac muscle of the rat when there were wide variations in the amount of whole dried meat in the animal's diet and when cardiac hypertrophy was produced secondary to hypertension after partial nephrectomy<sup>3</sup>.

### METHODS

The rats used in this study were of the Wistar stock and were maintained on a stock diet until they were between 60 and 70 days old. At that time they were subjected to a two stage operation, and immediately thereafter they were placed on one of the experimental diets listed in table 1. These diets differed only in the percentage of the whole dried meat which was the principal source of protein. To prepare the whole dried meat, lean meat was ground without loss of juice from the tissue, dried in a large steam-heated container and ground to a fine powder, it was found to be impossible to dry the ground meat at a constant temperature<sup>4</sup>. A quantitative record of the intake of food was not attempted. A maximum of eight rats was allowed to a cage, and food and water were always available. When the animals were killed, at varying intervals after operation, they were all in good health and were more than 4 months old.

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From the laboratory of physiologic chemistry, University of Virginia

This investigation was aided by a grant from the National Live Stock and Meat Board

1 (a) Cowan, D W. Proc Soc Exper Biol & Med **31** 417, 1934, (b) Am J Physiol **109** 312, 1934 (c) Bodansky, M., and Pilcher, J F. Proc Soc Exper Biol & Med **32** 597, 1935

2 Cowan, D W. Am Heart J **9** 378, 1934. Seecof, D P, Linegar, C R., and Myers, V C. Difference in Creatine Concentration of the Left and Right Ventricular Cardiac Muscles, Arch Int Med **53** 574 (April) 1934

3 Chanutin, A., and Ferris, E B, Jr. Experimental Renal Insufficiency Produced by Partial Nephrectomy. I Control Diet, Arch Int Med **49** 767 (May) 1932

4 We are indebted to the Valentine Meat Juice Company of Richmond, Va., for preparing this meat

Details of the operative procedure used to produce hypertension have been reported elsewhere<sup>3</sup> The experimental animals were anesthetized with ether, and subtotal nephrectomy was performed by placing a loop of thread around each pole of the left kidney and then tightening the loops to stop the circulation of two thirds or more of this kidney A week later the right kidney was excised Two types of control animals were used Unilaterally nephrectomized rats had the left kidney exposed and replaced, and after a week the right kidney was removed, non-nephrectomized rats were subjected to the procedure of exposure and replacement of both kidneys

The blood pressure in the carotid artery was taken before the rat was killed by exsanguination The ventricles of the heart were separated from the atria, blotted free from blood, weighed, cut up and dropped into acid The creatine content of the ventricles was determined by the method described by Rose, Helmer and Chanutin<sup>5</sup> for the determination of total creatinine

TABLE 1—*Composition of Diets in Grams per Hundred Grams*

Diet	Dried Meat	Lard	Starch	Yeast	Salt Mixture*	Cod Liver Oil
M 10	10	14	62	5	4	5
M 20	20	14	52	5	4	5
M 40	40	14	32	5	4	5
M 80	80	6		5	4	5

\* Osborne and Mendel

The degree of hypertrophy of the heart was expressed by the formula  $\frac{\text{heart weight}}{\text{surface area}} \times 100$ , which represents the number of milligrams of cardiac tissue per hundred square centimeters of surface area Similarly,  $\frac{\text{total creatine}}{\text{surface area}} \times 100$  was calculated to express the creatine content of the heart with reference to the surface area The surface area was calculated by the formula of Lee<sup>6</sup> from the weight of the animal at the time of killing

## RESULTS

Table 2 presents the maximum, minimum and average values for the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio, the  $\frac{\text{total creatine}}{\text{surface area}}$  ratio and the creatine concentration of the ventricles for each dietary group of control animals These values were highest in the rats fed the M 10 diet and lowest in the group fed the M 80 diet In general, however, the average values for each group closely approximated the average for the entire control series, and thus it appeared that the creatine concentration was not appreciably influenced by the percentage of whole dried meat in the diet The values for creatine concentration obtained in these experiments were unaccountably higher than were those obtained in previous analyses<sup>7</sup>

<sup>5</sup> Rose, W C , Helmer, O M , and Chanutin, A J Biol Chem **75** 543, 1927

<sup>6</sup> Lee, M O Am J Physiol **89** 24, 1929

<sup>7</sup> Chanutin, A , and Silvette, H J Biol Chem **80** 589, 1928

Table 3 compares the maximum, minimum and average values for the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio, the  $\frac{\text{total creatine}}{\text{surface area}}$  ratio and the creatine concentration of the ninety-three partially nephrectomized rats without hypertrophy with the same values for the thirty-two experimental animals with

TABLE 2—Data for Control Animals

	Diet	No of Animals	$\frac{\text{Heart Weight}}{\text{Surface Area}} \times 100$	$\frac{\text{Total Creatine}}{\text{Surface Area}} \times 100$	Creatine Concentration
			Mg	Mg	Mg per 100 Gm
Minimum	M 10	13	162	43	253
Maximum			185	63	388
Average			171	52	304
Minimum	M 20	16	146	43	232
Maximum			200	59	322
Average			176	51	287
Minimum	M 40	20	147	43	262
Maximum			202	59	330
Average			171	50	293
Minimum	M 80	21	145	37	232
Maximum			167	55	318
Average			164	45	273
Average for entire group			170	49	280

TABLE 3—Data for Partially Nephrectomized Animals

	No of Animals	$\frac{\text{Heart Weight}}{\text{Surface Area}} \times 100$	$\frac{\text{Total Creatine}}{\text{Surface Area}} \times 100$	Creatine Concentration	
		Mg	Mg	Mg per 100 Gm	
Minimum	93	132	39	243	$\frac{\text{Heart weight}}{\text{Surface area}}$ ratios in normal ranges for all diets
Maximum		198	64	356	
Average		174	51	290	
Minimum	32	186	44	240	$\frac{\text{Heart weight}}{\text{Surface area}}$ ratios above normal range for all diets
Maximum		300	83	357	
Average		220	62	286	

definite hypertrophy Cardiac hypertrophy was not considered definite unless the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio exceeded the highest value obtained in the same control dietary group The percentage of creatine concentration of the ventricles in the two groups of experimental animals is not appreciably different from the values obtained for normal rats, but the  $\frac{\text{total creatine}}{\text{surface area}}$  ratio increases when the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio increases

Chart 1 shows the relationship between the weight of the heart and the total creatine content in the control animals and in those which had been partially nephrectomized animals fed the various meat diets. The relatively high total creatine

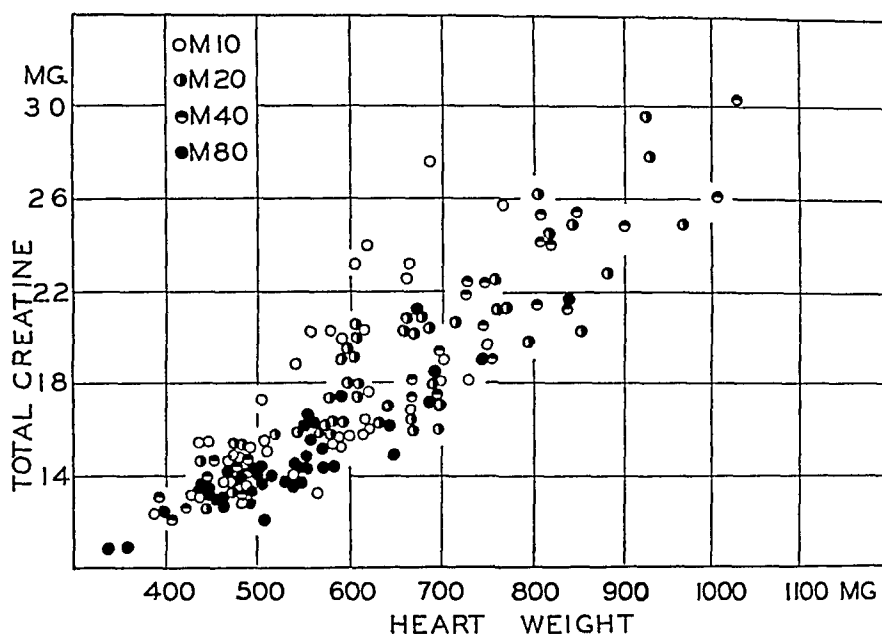


Chart 1—The relationship between the weight of the heart and the total creatine content in the control animals and in those which had been partially nephrectomized. The type of diet is indicated by the shading of the circle.

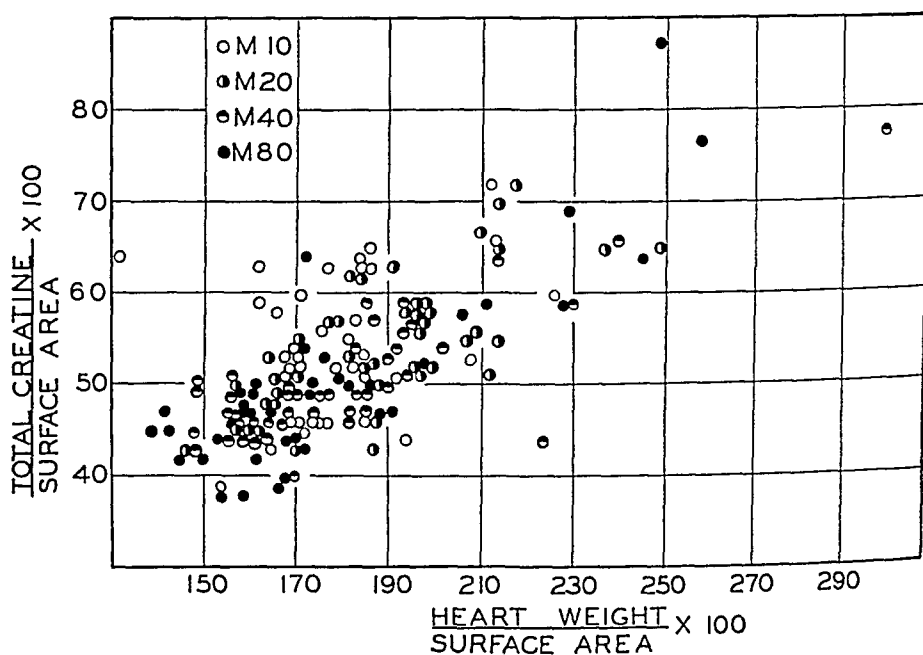


Chart 2—The relationship between the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio and the  $\frac{\text{total creatine}}{\text{surface area}}$  ratio for each animal in the entire series. The type of diet is indicated by the shading of the circle.

values for the animals on the M 10 diet are apparent, an explanation of this observation is difficult since the hearts were not hypertrophied and these animals received the diet which was lowest in creatine. It is obvious that there is a direct relationship between the weight of the heart and the total creatine content for the series as a whole.

The relationship between the  $\frac{\text{heart weight}}{\text{surface area}}$  ratio and the  $\frac{\text{total creatine}}{\text{surface area}}$  ratio of each animal in the entire series is presented in chart 2. It is seen that the majority of the creatine ratios were between 45 and 60 when the  $\frac{\text{heart weight}}{\text{surface area}}$  ratios were below 200. As the weight of the heart increases per unit of surface area, the total creatine for this unit of surface area also increases. In other words, the cardiac hypertrophy of experimental hypertension is accompanied by a roughly proportional increase in the total creatine content.

#### COMMENT

Hypertrophy of the heart can be best demonstrated by relating the weight of the heart to the surface area.<sup>8</sup> An analogous relationship is applicable to the creatine content of the heart by relating it to the surface area. The advantage in considering surface area for evaluating the creatine content of the heart can be illustrated by two control animals without cardiac hypertrophy, in which the total creatine values were 3.08 and 1.71 mg, respectively. When the respective areas of 547 and 306 square centimeters were considered in the ratio  $\frac{\text{total creatine}}{\text{surface area}} \times 100$ , the respective values were 0.56 and 0.56, which demonstrated that the creatine content per hundred square centimeters of surface area was the same regardless of the size of the animal. In a similar manner, calculation of the  $\frac{\text{total creatine}}{\text{surface area}}$  ratios for hypertrophied hearts demonstrated that the creatine content per hundred square centimeters of surface area was higher.

The value of interpreting the deposition of creatine in relation to the size of the animal can be emphasized by reference to two publications of Cowan. In his study of cardiac hypertrophy produced in rats by nutritional anemia, Cowan<sup>1a</sup> noted that the creatine content of the ventricles was the same for "anemic" rats and "litter mate" controls, but less for "size" controls. He concluded that "in the anemic rats the creatine was added to the heart at the normal growth rate, while the muscle mass increased more rapidly." However, if the creatine values of these groups are related to the surface areas, both size and litter mate control groups have almost identical average creatine values, and the hypertrophied hearts of anemic rats show a considerably higher

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8 Chanutin, A., and Barksdale, E. E. Experimental Renal Insufficiency Produced by Partial Nephrectomy. II. Relationship of Left Ventricular Hypertrophy, the Width of the Cardiac Muscle Fiber and Hypertension in the Rat, *Arch. Int. Med.* 52:739 (Nov.) 1933.



figure, indicating that this type of hypertrophy is accompanied by an increased deposition of creatine. In reporting the other investigation, Cowan<sup>1b</sup> expressed the belief that there was a loss of creatine from the heart in rats with acute and chronic hyperthyroidism and hypothyroidism. However, by similarly introducing the factor of size, it was found that appreciably less deposition of creatine occurred only in the animals with acute hyperthyroidism. Bodansky and Pilcher<sup>1c</sup> recently showed a lowered total creatine content in the hearts of rats with hyperthyroidism, but the  $\frac{\text{total creatine}}{\text{surface area}}$  ratios of these hearts showed no appreciable difference between the control and the experimental animals.

#### SUMMARY AND CONCLUSIONS

The creatine content of the hearts of intact, unilaterally nephrectomized and partially nephrectomized rats, with and without cardiac hypertrophy, was determined after feeding diets containing 10, 20, 40 and 80 per cent of whole dried meat.

Within the experimental conditions of this study, it seems that the creatine concentration of the ventricles is independent of the percentage of creatine in the diet. Further it appears that the total creatine content of the heart increases in approximately direct proportion as the size of the heart increases, whether normally or as the result of experimental hypertension, hence it follows that the creatine concentration remains fairly constant. The creatine content of the heart per unit of surface area is increased in hypertensive hypertrophy. This indicates that the increase in the weight of the heart in hypertrophy resulting from hypertension is due to an increase in muscular tissue.

# COOPERATIVE CLINICAL STUDIES IN THE TREATMENT OF SYPHILIS CARDIOVASCULAR SYPHILIS

I UNCOMPLICATED SYPHILITIC AORTITIS ITS SYMPTOMATOLOGY,  
DIAGNOSIS, PROGRESSION AND TREATMENT

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Probably no syphilitic involvement of the human body is more frequently overlooked than that of the cardiovascular system. Of all types, uncomplicated syphilitic aortitis undoubtedly is the most frequently ignored. This is due, to some extent, to a longer or shorter silent period of the disease and also to insufficient attention on the part of the physician to premonitory signs and symptoms. As one of us<sup>1</sup> recently said "The medical students crowd about the cor bovinum and the hat-box aneurysm, they observe with enthusiasm the thrill, the buzzing and whirring, the heave, the sound of the pistol shot. Seldom indeed does one find an equal degree of absorption or an equal frequency of demonstration of the still, small signs and symptoms of the preventable onset of syphilitic cardiovascular disease." Many pathologists, among them Langer,<sup>2</sup> Guldberg<sup>3</sup> and Warthin,<sup>4</sup> have emphasized the high percentage

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The names with an asterisk represent members of the United States Public Health Service, the names without an asterisk represent members of the Cooperative Clinical Group

From the syphilis clinics of the Western Reserve University, the Johns Hopkins University, the Mayo Clinic, the University of Pennsylvania and the University of Michigan, assisted by the United States Public Health Service, with the financial support of an anonymous donor

1 Stokes, J H. Modern Clinical Syphilology, ed 2, Philadelphia, W B Saunders Company, 1934, pp 1018, 1923, 1057 and 1059

2 Langer, E. Die Häufigkeit der luetischen Organveränderungen insbesondere der Aortitis luetica, München med Wchnschr **73** 1782, 1926

3 Guldberg, G. Ueber Sektionsbefunde bei Syphilitikern, Arch f Dermat u Syph **166** 730, 1932

4 Warthin, A S. The Lesions of Latent Syphilis, South M J **24** 273, 1931

of syphilitic involvement of the cardiovascular apparatus as revealed at autopsy in from 55 to 86 per cent of all patients with syphilis. Moreover, in Guldberg's material from 8,235 autopsies there was evidence of syphilis in 481 cases, or 5.8 per cent, and it was the cause of death in 349. In 58 per cent of the cases of syphilis there was evidence of vascular syphilis. In 261, or 54 per cent, it was the primary condition, and of these it was the cause of death in 218. Stokes<sup>1</sup> said "From the pathologic physiology of syphilis, it is difficult to understand how the heart and great vessels can ever escape involvement." And yet, how many patients are brought to autopsy, and there for the first time cardiovascular syphilis is revealed!

Are the requirements for a diagnosis too rigorous? Are diagnostic methods as yet too crude? Is the acumen of the clinician at fault? Perhaps all three play a part, and there is no doubt that a higher percentage of cases would be revealed by more thorough history-taking and examinations. At any rate, a large proportion of cardiovascular syphilis is discovered after the damage is done. Because of the generally recognized necessity for diagnosing cardiovascular syphilis in its earliest stage, the members of the Cooperative Clinical Group have examined the cardiovascular data for 10,614 syphilitic patients who were treated for more than six months. This material comprises observations on cases of syphilis in early and in late stages and of latent syphilis. However, the group of patients with syphilis in a late stage is limited principally to those with syphilitic involvement of the central nervous system or the cardiovascular system.

#### MATERIAL

There is included in table 1 the number of cases in which the diagnosis was uncomplicated syphilitic aortitis, aortic regurgitation, aortitis with aneurysm or myocarditis, showing the frequency of cardiovascular involvement in 6,253 patients with syphilis in a late stage<sup>5</sup> or latent syphilis who had been under observation or treatment for six months or longer. Of the entire group, there were 619 cases, or 9.9 per cent, in which cardiovascular syphilis was manifested on admission or subsequently developed. The largest group was that of cases of uncomplicated syphilitic aortitis and included 307 cases, or 4.9 per cent, the second was that of cases of aortic regurgitation, with 257 cases, or 4.1 per cent, the third, that of cases of aortitis with saccular aneurysm, comprising 73 cases, or 1.2 per cent, and a small group of 53 cases or 0.8 per cent, of myocarditis.

There were 326 patients with uncomplicated syphilitic aortitis, 307 of whom were admitted with syphilis in a late stage or latent syphilis for whom the diagnosis was made on admission or in whom the condition developed subsequently and 19 of whom were admitted with the early stage of syphilis and acquired uncomplicated syphilitic aortitis while under observation or treatment.

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<sup>5</sup> The cases of late syphilis are exclusive of those of benign late syphilis or syphilis of bone or the skin, syphilis of the upper respiratory tract, glands, eyes or viscera, other than cardiovascular syphilis. Therefore, the percentages represent only the relative frequency of cardiovascular manifestations in the race and sex groups considered.

OBSERVATIONS

*Influence of Sex, Race and Age*—The influence of race and sex on the frequency of uncomplicated syphilitic aortitis may be observed in table 1. In white males and females, the frequency was practically the same, being 3.7 and 3.5 per cent, respectively. For Negroes the frequency was 13.8 per cent in males and 8 per cent in females. The observation that the Negro is more prone to cardiovascular syphilis has been confirmed in the material of the Cooperative Clinical Group, this manifestation being nearly three times more frequent in Negroes than in white persons. This greater frequency of cardiovascular involvement

TABLE 1—*Influence of Race and Sex on the Frequency of Syphilitic Cardiovascular Involvement in 6,253 Patients Admitted with Late<sup>5</sup> or Latent Syphilis*

Sex and Race	Cardiovascular Diagnosis on Admission								Patients with Cardiovascular Involvement*		Patients Admitted with Late <sup>5</sup> or Latent Syphilis	
	Uncomplicated Syphilitic Aortitis		Aortic Regurgitation		Myocarditis		Aortitis with Aneurysm		No	Per cent age	No	Per cent age
	No	Per cent age	No	Per cent age	No	Per cent age	No	Per cent age				
Male												
White	134	3.7	135	3.7	24	0.7	31	0.9	293	8.1	3,602	100.0
Negro	66	13.8	58	12.1	15	3.1	30	6.3	148	31.0	478	100.0
Total	200	4.9	193	4.7	39	1.0	61	1.5	441	10.8	4,080	100.0
Female												
White	52	3.5	38	2.6	6	0.4	6	0.4	90	6.1	1,487	100.0
Negro	55	8.0	26	3.8	8	1.2	6	0.9	88	12.8	686	100.0
Total	107	4.9	64	2.9	14	0.6	12	0.6	178	8.2	2,173	100.0
Total												
White	186	3.7	173	3.4	30	0.6	37	0.7	383	7.5	5,089	100.0
Negro	121	10.4	84	7.2	23	2.0	36	3.1	236	20.3	1,164	100.0
Grand total	307	4.9	257	4.1	53	0.8	73	1.2	619†	9.9	6,253	100.0

\* If a patient was admitted with a diagnosis of more than one cardiovascular involvement the case was included in each diagnosis but is counted as 1 case in the total.

† This does not include 23 patients who were admitted with early syphilis and in whom cardiovascular involvement developed.

in the Negro has often been attributed to the more strenuous labor performed by the Negro man than by the white man. However, the material of the Cooperative Clinical Group did not contain any information with regard to the occupation of the patients.

Of the 326 patients in whom uncomplicated syphilitic aortitis was detected, 9 per cent had this involvement before the age of 30. In patients in the age group from 35 to 45 the highest incidence was found, 39 per cent. There was a small group (3 per cent) in whom this late manifestation of syphilis appeared after the age of 65.

*Early Detection of Uncomplicated Syphilitic Aortitis*—Several reports of very early cardiovascular involvement in persons with syphilis

have been made Reid <sup>6</sup> reported a case in which a young man infected in June gave definite evidence of aortic involvement by August and enough signs for a positive diagnosis by September, three months after infection Brooks <sup>7</sup> observed a case in which death resulted from perforation of the aorta just above the valves before the secondary eruption was fully developed

In the present material of 186 cases of uncomplicated syphilitic aortitis in which the duration of the syphilitic infection was known, the process had developed to the point of detection in 19, or 10 per cent, in less than five years There was no case in which the syphilitic infection was of less than one year's duration In 3 instances this complication was diagnosed in the second year of infection One of the patients had not received any treatment prior to the detection of uncomplicated syphilitic aortitis, 1 had received from seven to twelve injections of an arsenical with an interim course of a heavy metal, intermittently given, and in the third case twenty-six injections of an arsenical with an interim course of a heavy metal had been administered intermittently However, in these cases there was a questionable diagnosis of mild aortitis In the three year period, 3 patients with this complication were seen One patient had not been treated, 1 had received from thirteen to eighteen injections, and 1, twenty-five injections, of an arsenical, with an interim course of a heavy metal, both irregularly given In the four year period, 7 patients with this complication were seen Four of the patients had not had any treatment 1 had received from one to six injections of an arsenical, with an interim course of a heavy metal, irregularly given, and 2 had received from seven to twelve injections of an arsenical, with an interim course of a heavy metal, likewise irregularly given In the five year period, there were 6 cases One patient had not been treated, 1 had received from one to six injections, 1, from thirteen to eighteen injections, 1, from nineteen to twenty-four injections, and 2, twenty-five or more injections, of an arsenical, with an interim course of a heavy metal, all irregularly given In this series it was noted that good treatment of syphilis in the early stage prevented the development of uncomplicated syphilitic aortitis within the first five years of the disease

*Observations on the Blood and Spinal Fluid*—Serologic tests of the blood within ten days before or after the detection of uncomplicated syphilitic aortitis were made in 255 cases, and tests of 72 per cent of this number gave positive results Any degree of positivity of the reaction of the blood serum was considered to be a positive reaction

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6 Reid, William D    Specific Aortitis, Boston M & S J **183** 67 and 105, 1920

7 Brooks, Harlow    Syphilis of the Heart, Am J Syph **5** 217, 1921

The effect on the Wassermann reaction of the blood of treatment received prior to the detection of uncomplicated syphilitic aortitis was studied. Of the cases of syphilis in which no treatment or an unknown amount of treatment had been given, there was a positive Wassermann reaction of the blood in 83 per cent at the time of recognition of the cardiovascular syphilis. When more than eighteen injections of an arsenical, with an interim course of a heavy metal, had been given prior to the detection of the uncomplicated syphilitic aortitis, the percentage of cases in which there was a positive Wassermann reaction of the blood dropped to 52.

Numerous studies emphasizing the close relationship between cardiovascular syphilis and involvement of the central nervous system have been made. Of the 191 cases of uncomplicated syphilitic aortitis in which lumbar punctures were made within a month of the detection of aortitis, unquestionable abnormalities of the spinal fluid were present in 93, or 49 per cent. In this computation the reaction was classified as positive only when there was frank evidence of involvement of the spinal fluid. The examination of the spinal fluid consisted of a Wassermann test, a test for globulin, a colloidal gold test and a cell count. While the number of cases is small, it is noted that the percentage of such positive tests among white women was more than twice as high as that noted among Negro women. This difference, while significant, was not so marked between white and Negro men, being 63 and 43 per cent, respectively.

*Diagnostic Methods*—The principal symptoms and signs in the records of the Cooperative Clinical Group of cases of cardiovascular syphilis with a diagnosis of uncomplicated syphilitic aortitis are given in the order of their importance.

- 1 Teleroentgenographic and fluoroscopic evidence of aortic dilatation
- 2 A tympanic, bell-like tambour accentuation of the aortic second sound
- 3 A history of circulatory embarrassment
- 4 Increased retromanubrial dulness
- 5 Progressive cardiac failure
- 6 Substernal pain
- 7 Paroxysmal dyspnea<sup>8</sup>

It is observed that in patients known to be syphilitic and with no evidence of mitral disease these signs and symptoms are similar to those on which Carter and Baker<sup>9</sup> based the criteria for the diagnosis of

<sup>8</sup> Two other signs of value were frequent enough to be mentioned, systolic murmur in the aortic valve area and visibly or palpably increased pulsation in the episternal notch.

<sup>9</sup> Carter, Edward P., and Baker, Benjamin M., Jr. Certain Aspects of Syphilitic Cardiac Disease, *Bull. Johns Hopkins Hosp.* 48: 315, 1931.

aortic regurgitation and aneurysm This was subsequently reported by Moore, Danglade and Reisinger,<sup>10</sup> who limited their study to cases of uncomplicated syphilitic aortitis The latter authors expressed the opinion that the presence of three or more of these signs and symptoms in a syphilitic patient under 50 years of age, free from mitral disease and with no hypertension, is strong evidence for the diagnosis of uncomplicated syphilitic aortitis and that the presence of any two of them renders the diagnosis probable

*Roentgen Findings on Admission or on Progression*—There has been much discussion in the literature as to the value of roentgen examination in diagnosing uncomplicated syphilitic aortitis Some clinicians do not even employ the method Undoubtedly there is a silent stage of aortitis during which the roentgen rays may be of little or no value On the other hand, there are certain cases in which roentgen examination may add much presumptive evidence to other findings

*Concomitant Syphilis*—One of the objectives of this study was to ascertain the frequency with which cardiovascular syphilis coexists with other manifestations of the disease It is possible that the frequency with which syphilis involves not only the circulatory system but other systems may be of great aid in leading the physician to suspect and possibly to identify other manifestations as syphilitic

Of the 326 cases studied, nothing more than uncomplicated syphilitic aortitis was evident in 160, evidence of the disease having attacked other organs or systems in the body was noted in 166 Apparently concomitant involvement of the skin is infrequent, as it was observed in only 4 per cent of the cases, similarly, osseous involvement was noted in only 5 per cent, and involvement of the viscera other than the cardiovascular organs occurred in only 2 per cent Ocular involvement other than that associated with syphilis of the central nervous system was noted in 0.6 per cent of the cases The most important fact noted was the frequency of involvement of the central nervous system in connection with cardiovascular syphilis It has been mentioned in a previous paragraph that among 191 cases of uncomplicated syphilitic aortitis in which an examination was made of the spinal fluid the test was positive in 93, or 49 per cent With combined clinical and laboratory findings it was estimated that of the 326 cases there was evidence of involvement of the central nervous system in 146, or 45 per cent In 25 per cent of the 326 cases the involvement of the central nervous system was parenchymatous, a finding that has been emphasized in the past by

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10 Moore, J. E., Danglade, J. H., and Reisinger, J. C. Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm, *Arch Int Med* 49:753 (May) 1932

various writers, particularly by Stokes<sup>1</sup> and Moore<sup>11</sup> of this group. In 9 per cent of the cases there was evidence of asymptomatic syphilis of the central nervous system, in 3 per cent, of meningeal neurosyphilis, in 5 per cent, of vascular neurosyphilis, and in 5 per cent, of diffuse meningovascular neurosyphilis. It cannot be too strongly emphasized that in the presence of cardiovascular syphilis particular stress should be laid on the confirmation or the exclusion of involvement of the central nervous system, and, vice versa, in the presence of syphilis of the central nervous system the physician should exercise extreme care to make sure that he is not dealing with cardiovascular syphilis as well. This is particularly true when, as will be seen later, the factor of treatment is brought into the picture. If the physician should institute some of the accepted measures for treatment of syphilis of the central nervous system which ordinarily are used in the beginning of treatment, the same measures might be considered most radical from the standpoint of treatment of cardiovascular involvement and might lead to disastrous results.

*Prophylaxis of Cardiovascular Syphilis by Treatment of Syphilis in the Early Stages*—Of 3,641 cases in which treatment was given during the early stages of the disease, cardiovascular syphilis developed subsequently in 26 cases, or less than 1 per cent. In most of the cases (22) only uncomplicated syphilitic aortitis developed and there was no further progression. When an adequate amount of treatment had been given during the early stages of syphilis, regardless of whether the treatment was given regularly or irregularly, aortic regurgitation or aneurysm did not develop in a single case. This emphasizes the value of treatment of syphilis in the early stage in the prevention of late and crippling manifestations of the disease.

Since 71 per cent of the cases of early syphilis, however, have not been followed for more than three years, there is a strong probability that in many of these cases cardiovascular syphilis will be detected as the period of observation is extended. In this series of cases of early syphilis in which treatment had been received, 935 patients were followed for a period of from three to ten years, and in 15, or 1.6 per cent, cardiovascular syphilis developed. Of 105 patients followed from ten to twenty years, cardiovascular syphilis developed in 7, or 6.7 per cent. The detailed findings as related to treatment in the early stages of syphilis are given in table 2. It is apparent from these findings that the patient adequately and regularly treated for early syphilis and followed from three to twenty years after infection will be almost exempt

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<sup>11</sup> Moore, J. E. *Modern Treatment of Syphilis*, Springfield, Ill., Charles C. Thomas, 1933, p. 292.



from cardiovascular involvement. Moreover, there was no case of aneurysm or of aortic regurgitation in the group.

*Outlook With Treatment*—With the exception of a few writers it seems to have been the consensus, in the United States at least, that the outlook in cases of uncomplicated syphilitic aortitis is grave. On the

TABLE 2—*Prophylactic Value of Early Treatment in the Prevention of Cardiovascular Syphilis*

Amount* and Scheme of Treatment During Early Syphilis	Length of Time Patient Was Followed from Time of Infection	Patients with Early Syphilis	Patients in Whom Cardiovascular Syphilis Developed Subsequently			
			Uncomplicated Syphilitic Aortitis	Aortic Regurgitation	Myocarditis	Total
Inadequate and irregular	Less than 3 yr	334	1			1
	3 to 10 yr	216	8	1		9
	10 to 20 yr	38	6†	1	1	6
	20 yr and more	1	1			1
	Total	589	16	2	1	17
Inadequate and regular	Less than 3 yr	1,293		1		1
	3 to 10 yr	197	1			1
	10 to 20 yr	16				
	20 yr and more	2				
	Total	1,508	1	1		2
Adequate and irregular	Less than 3 yr	76				
	3 to 10 yr	193	4			4
	10 to 20 yr	41	1			1
	20 yr and more	2				
	Total	318	5			5
Adequate and regular	Less than 3 yr	893	1			1
	3 to 10 yr	323	1			1
	10 to 20 yr	10				
	20 yr and more					
	Total	1,226	2			2
Total	Less than 3 yr	2,596	2	1		3
	3 to 10 yr	935	14	1		15
	10 to 20 yr	105	7†	1	1	7
	20 yr and more	5	1			1
	Total	3,641	24	3	1	26

\* Less than twenty injections of arsphenamine, with an interim course of a heavy metal, constitutes inadequate treatment, more than this amount constitutes adequate treatment.

† In 1 case the condition progressed to aortic regurgitation, and in 1, to myocarditis.

other hand, Moore and Metildi<sup>12</sup> in this country and Grant<sup>13</sup> in England particularly emphasized the fact that treatment may greatly change the prognosis.

Several factors should be taken into consideration when one attempts to attribute prolongation of life to the effectiveness of varying amounts

12 Moore, J. E., and Metildi, P. F. Uncomplicated Syphilitic Aortitis. Diagnosis, Prognosis and Treatment, *Arch Int Med* 52:978 (Dec) 1933.

13 Grant, R. T. After Histories for Ten Years of One Thousand Men Suffering from Heart Disease. A Study in Prognosis, *Heart* 16:275, 1933.

of therapy administered after the detection of cardiovascular syphilis. These are first, whether the patient's physical condition on admission permitted this type of therapy and, second, whether the patient remained under treatment for a sufficient length of time to permit evaluation of the therapy. In order to overcome these two distorting factors, the cases which were followed for less than one year, whether the patient died or lapsed from treatment, were eliminated from the tabulation of the end-results of treatment. This precaution having been taken, the periods of treatment and observation for both the living and the dead patients were determined. Since proportionately the same numbers of living and dead patients had been followed throughout each of the periods of treatment and observation, it can be assumed that the pro-

TABLE 3—*Effectiveness of Treatment After Detection of Uncomplicated Syphilitic Aortitis in the Prolongation of Life\**

Amount of Treatment After Detection of Aortitis†		Living		Dead, All Causes		Average Duration of Life After Detection of Aortitis, Months		
Arsenical‡	Heavy Metal	Number	Percentage	Number	Percentage	Living	Dead	Total
Little	Little	49	76.6	15	23.4	53	34	49
Little	Much	27	77.1	8	22.9	56	56	56
Much	Little	35	87.5	5	12.5	66	56	65
Much	Much	114	89.1	14	10.9	60	85	62
Total		225	84.3	42	15.7	59	58	59

\* This includes observations only on cases in which treatment or observation was continued for one year or more.

† The amount of treatment includes that received from the time of detection of the uncomplicated syphilitic aortitis to death, or, if the patient was living, to the end of the observation.

‡ Little for injections of an arsenical means less than thirteen injections (inadequate), and much, thirteen injections or more (adequate). Little for heavy metal means less than twenty injections or weeks of rubs (inadequate) and much, twenty or more injections or weeks of rubs (adequate).

longation of life was to some extent dependent on the varying amounts of treatment. Adequate treatment was considered to be thirteen or more injections of an arsenical, with twenty or more injections of a heavy metal, administered after the detection of the uncomplicated syphilitic aortitis.

In table 3 it will be observed that an adequate amount of both the arsenical and the heavy metal was essential in obtaining the greatest prolongation of life (eighty-five months) from the time of detection of uncomplicated syphilitic aortitis to death. When an inadequate amount of either drug was administered in combination with an adequate amount of the other, the average duration of life dropped from eighty-five to fifty-six months. When little or no modern therapy was given after the detection of the uncomplicated syphilitic aortitis, the average duration of life was only thirty-four months.

*Outcome from the Standpoint of Adequate and Inadequate Therapy*—In table 4 the outcome for patients who were living at the time of the last check-up is given in terms of freedom from symptoms, progression of symptoms and signs and development of graver types of cardiovascular involvement, and for those who had died, an indication of whether or not the cause of death was the result of the cardiovascular condition having progressed to aortic regurgitation or aneurysm

Treatment is indicated as adequate or inadequate and the amount includes that which was given from the detection of uncomplicated

TABLE 4—*Outcome in Cases of Uncomplicated Syphilitic Aortitis\**

Outcome of Last Observation	Amount of Arsenical Treatment from Detection to End of Observation					
	Inadequate†			Adequate		
	Number	Per centage	Duration of Life, Mo	Number	Per centage	Duration of Life, Mo
<b>Living</b>						
Free from symptoms, no progress	50	49.0	51	104	63.0	56
Progress in signs or symptoms	9	8.8	11	27	16.4	72
Aortic regurgitation or aneurysm ‡	6	5.9	56	10	6.1	98
No data (living at last report)	14	13.7	25	5	3.0	50
<b>Total living</b>	<b>79</b>	<b>77.4</b>	<b>53</b>	<b>146</b>	<b>88.5</b>	<b>62</b>
<b>Dead</b>						
Died of aneurysm or aortic regurgitation	1	1.0	58	1	0.6	92
Died of other forms of cardiovascular syphilis	7	6.9	34	2	1.2	22
Died probably of cardiovascular syphilis				1	0.6	67
Other known causes or cause of death not reported	15	14.7	45	15	9.1	84
<b>Total dead</b>	<b>23</b>	<b>22.6</b>	<b>42</b>	<b>19</b>	<b>11.5</b>	<b>77</b>
<b>Grand total</b>	<b>102</b>	<b>100.0</b>	<b>51</b>	<b>165</b>	<b>100.0</b>	<b>63</b>

\* This includes cases of patients followed for one year or more after the detection of uncomplicated syphilitic aortitis

† Less than thirteen injections of arsphenamine, with an interim course of a heavy metal, constituted inadequate treatment, more than this amount was adequate

‡ The amount of treatment includes that administered down to the time of progression

syphilitic aortitis to the termination of the case. Adequate treatment is defined as including thirteen or more injections of an arsenical, with an interim course of a heavy metal, and inadequate treatment includes less than thirteen injections, with an interim course of a heavy metal. Of the patients who were inadequately treated, 77 per cent were still living, with an average duration of fifty-three months since the detection of cardiovascular involvement. Of the patients who were adequately treated, 89 per cent were still living, and the average duration of life was increased to sixty-two months. Twenty-three per cent of the patients inadequately treated died, and the average duration of life was forty-two months, while 12 per cent of the adequately treated

patients died, and the average duration of life was seventy-seven months. In other words, treatment almost doubled the duration of life of persons with a condition that is considered to have a grave outlook.

It was found that 49 per cent of the patients inadequately treated were still living and free from symptoms and that there had been no progression of the uncomplicated syphilitic aortitis, whereas among those adequately treated, 63 per cent were still living and free from symptoms. The length of time over which these patients were followed after the detection of uncomplicated syphilitic aortitis was slightly higher for the adequately treated patients, being fifty-six months as compared with fifty-one months for patients inadequately treated. Adequate therapy also appeared to be more successful in the prevention of death from cardiovascular syphilis than did inadequate treatment after the detection of uncomplicated syphilitic aortitis. In 24 per cent of the cases in which treatment was adequate cardiovascular syphilis was either definitely or probably the cause of death, as compared with an incidence of 79 per cent in cases in which the patient had been inadequately treated. Thus a review of the cases followed to death indicated that adequate therapy for uncomplicated syphilitic aortitis not only practically doubled the duration of life but also lessened the frequency of cardiovascular syphilis as the cause of death.

*Influence of Doses of Arsenical on Outcome*—Apparently it is true that adequate treatment with an arsenical and an interim course of a heavy metal is of great value in the management of uncomplicated syphilitic aortitis. Nevertheless there is much discussion among syphilologists and internists as to what constitutes proper treatment. Some physicians even prefer to exclude arsphenamine entirely, others believe that if the arsenical, especially neoarsphenamine, is administered cautiously and in small doses a proper and beneficial action will result.

An analysis of the effect of the size of the dose was made in a total of 166 cases in which arsphenamine and neoarsphenamine were the predominant arsenicals used in treatment. While small doses appear to have had little effect in preventing further progression, there was a definite prolongation of life in such cases. There were 121 cases in which large doses were administered with an average duration of life of fifty-three months, while in the 45 cases in which small doses were administered, the average duration of life was seventy-three months. Thus, there is indicated a greater prolongation of the average duration of life with the small dose than with the large one. The data suggest that in the treatment of uncomplicated syphilitic aortitis the physician will wisely limit his use of arsenicals to small doses in an effort to prolong life. It is not possible to overwhelm the syphilitic process in the aorta by the use of large doses of an arsenical. Moreover, the

unwise use of large doses may bring on what Wile<sup>14</sup> termed a therapeutic paradox. This is especially true if the arsenical is employed at the beginning of treatment. There is at first a temporary improvement in the patient's condition, but it may eventually result in so much distortion of the aortic walls and leaflets than an even more serious condition will remain than that from which the patient suffered originally. With the use of smaller doses there is more opportunity for a gradual "healing sclerosis" of the walls of the vessel. Or, as Stokes<sup>1</sup> stated: "A progressive disability is exchanged for an arrested and static one."

*Effect of Treatment on Further Progression*—Table 5 indicates that of the 267 patients followed for one year or more after the detection of uncomplicated syphilitic aortitis, 183, or 69 per cent, had received no arsenical treatment or only a little heavy metal therapy previous to the detection of uncomplicated syphilitic aortitis, 19, or 7 per cent, of the total number had received nineteen or more injections of an arsenical, with an interim course of a heavy metal. Two of these patients, however, had syphilis in the early stage, and only 1, for whom there was a questionable diagnosis of aortitis, had received regular treatment of twenty or more injections of an arsenical, with an interim course of a heavy metal, for the early stage of syphilis. In the other case, twenty-four injections had been given during the early stage, but there were frequent lapses throughout the course of treatment.

No further progression from uncomplicated syphilitic aortitis was noted in 90 per cent of the 267 cases.

Progression of uncomplicated syphilitic aortitis to aortic regurgitation occurred in 71 per cent of the cases, to myocarditis in 22 per cent, and to aortitis with saccular aneurysm in 15 per cent. In the group of patients in whom the condition advanced to aortic regurgitation (19), it is remarkable that 15 had received no treatment or only a little heavy metal previous to the development of the uncomplicated syphilitic aortitis. After the detection of the syphilitic cardiovascular involvement, advancement to aortic regurgitation occurred in 7 of these 19 patients after they had received more than eighteen injections of an arsenical, with an interim course of a heavy metal. Of the 6 patients in whom the condition advanced to myocarditis, only 1 had had previous therapy, after the diagnosis, 3 of this group had received more than eighteen injections of an arsenical, with an interim course of a heavy metal. Of the 4 patients in whom the condition advanced to aortitis with saccular aneurysm, 3 had not received any previous treatment, though all 4 had had thirteen or more injections of an arsenical, with an interim

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14 Wile, U. J. Treatment of Syphilitic Liver and Heart, *Am J M Sc* 164:415, 1922, Principles Underlying Treatment of Cardiovascular Syphilis, *Am Heart J* 6:157 (Oct) 1930.

course of a heavy metal, from the time of the detection of an uncomplicated syphilitic aortitis to the time of progression, and 3 of the 4 had had more than eighteen doses

TABLE 5—*Effect of Treatment on Further Progression of Uncomplicated Syphilitic Aortitis*

		Arsenical Treatment Before Detection													
Arsenical Treatment* from Detection		None, or Heavy Metal Only	Doses					Total							
			1-6	7-12	13-18	19-24	25 or More								
No further progression															
Living															
None, or heavy metal only	12	3	3	3	2	2	25								
1 to 6 doses	11	3		2	1		17								
7 to 12 doses	23	2	4	1		1	31								
13 to 18 doses	29	6	6	2		3	46								
19 to 24 doses	20	2	2		3	2	29								
25 doses or more	46	8	2	3			59								
Total	141	24	17	11	6	8	207								
Dead all causes															
None, or heavy metal only	4		2		1	1	8								
1 to 6 doses	3	1	1			1	6								
7 to 12 doses	8	1					9								
13 to 18 doses	3	3	2				8								
19 to 24 doses	3	1					4								
25 doses or more	6	1					7								
Total	27	7	5		1	2	42								
Type of Progression and Arsenical Treatment Previous to Detection															
Progression Arsenical Treatment from Detection to Progression	Aortic Regurgitation				Myo carditis		Aortitis with Aneurysm		Progressions, Total Cases				Grand Total		
	None, or Heavy Metal Only	1-6 Doses	13-18 Doses	19-24 Doses	25 Doses or More	None, or Heavy Metal Only	25 Doses or More	None, or Heavy Metal Only	1-6 Doses	None, or Heavy Metal Only	1-6 Doses	13-18 Doses		19-24 Doses	25 Doses or More
Living															
None, or heavy metal only															
1 to 6 doses	2		1	1	1		1			2		1	1	1	5
7 to 12 doses	1									1					1
13 to 18 doses	3									3					3
19 to 24 doses	1					1		1		3					3
25 doses or more	5					2				6					6
Total	12		1	1	1	3	1	1		15		1	1	1	18†
Dead															
None, or heavy metal only						1				1					1
1 to 6 doses	1									1					1
7 to 12 doses	1									1					1
13 to 18 doses		1				1		1		1	2				3
19 to 24 doses	1							2		2					2
25 doses or more															
Total	3	1				2		2	1	6	2				8†

\* The amount of treatment is that received from the time of detection of uncomplicated syphilitic aortitis to the end of the observation

† In 26 cases there were twenty nine progressions

Forty-two, or 16 per cent, of the 267 patients died. The cardiovascular syphilis was definitely or probably the primary cause of death of 12, 2 died of an aneurysm or aortic regurgitation and 9 of some other

form of cardiovascular syphilis, and cardiovascular syphilis was the probable cause of death of 1. All these patients had been irregularly or poorly treated previous to their admission to the clinic with syphilis in a late stage.

Probably the most striking fact that is brought out in table 5 is the greater absence of progression from uncomplicated syphilitic aortitis among patients who had received more than six injections of an arsenical, with an interim course of a heavy metal, before the clinical detection of the cardiovascular syphilis.

It is interesting to note in table 6 that 82 per cent of the patients were followed for one year or longer after the detection of uncomplicated syphilitic aortitis, 63 per cent for two years or longer and 38 per cent for five years or longer. The highest percentage of instances in which the condition advanced to graver forms of cardiovascular syphilis occurred among the patients followed from two to five years.

TABLE 6—*Progression of Cases of Uncomplicated Syphilitic Aortitis in Indicated Years of Treatment and Observation*

Years of Treatment and Observation from Detection of Aortitis	Cases Completing Indicated Years of Treatment- Observation Life		Cases in Which Progression Occurred	
	Number	Percentage	Number	Percentage
Less than 1 yr	326	100.0	2	0.6
1 to 2 yr	267	81.9	6	2.2
2 to 5 yr	204	62.6	13	6.4
5 to 10 yr	96	29.4	3	4.0
10 to 15 yr	29	8.9	2	

*Symptomatic Relief*—Of the 326 patients whose cases comprise this study, 173, or 53 per cent, complained of symptoms of cardiovascular syphilis. Of the cases in which thirteen or more injections of an arsenical, with an interim course of a heavy metal, were administered, symptomatic relief was achieved in 67 per cent as compared with only 22 per cent in which no specific treatment was given and 38 per cent in which less than thirteen arsenical injections, with an interim course of a heavy metal, were given. Comparable forms of medical regimen for the treatment of cardiac disease were used in all cases, regardless of whether antisyphilitic treatment was administered. Of the 153 cases in which the condition was reported as asymptomatic, symptoms developed in 16 per cent with subsequent improvement in 52 per cent following therapy.

A patient was considered to have had symptomatic relief if one, or more, of the severe symptoms was relieved and if there was no evidence of progression. In determining the proportion of persons experiencing symptomatic relief, the number of patients was not limited to those who

had been under observation and treatment for a year or more, because it was felt that symptomatic relief can well be indicated in a period much less than one year

#### TREATMENT

In the light of the data furnished, the important point which should be brought out is that of prophylactic treatment of this disease, accepting the dictum that probably most persons with the late stage of syphilis have a pathologic change in the aorta, as has been revealed at autopsy. There were only 2 clinical cases of this complication, in one of which it was questionable, observed in patients who during the early stage of syphilis had been adequately and regularly treated with more than twenty injections of an arsenical, with an interim course of a heavy metal. Realizing, as one must, that cardiovascular syphilis is one of the most frequent causes of disability and death from syphilis, the physician by thorough and continuous treatment with an arsenical and a heavy metal in the early stage of syphilis, should prevent the beginning of this grave complication in his patient. The treatment should consist of at least from twenty to thirty injections of an arsenical drug and an appropriate amount of heavy metal, according to the standardization of treatment of syphilis in the early stage, published by the Cooperative Clinical Group<sup>15</sup>

Once the diagnosis of syphilitic aortitis is established, the physician must be guided by the conditions found. Under no circumstances should severe reactions to treatment be risked. These might result in a local Herxheimer reaction, or again, with too large doses of an arsenical, there might be danger of a therapeutic paradox, as we suggested in certain cases of this series. In fact, the study showed that the slowly healing sclerosis of Stokes, with its static disability, was better achieved with small doses of an arsenical than with larger doses and added an average of twenty months to the life of a patient. Though the study does not directly indicate it, the average patient with uncomplicated syphilitic aortitis, in view of the aforementioned observations, should have a preliminary course of treatment with injections of either a soluble or an insoluble preparation of a heavy metal over a period of two or three months. Potassium iodide may be given by mouth at the same time. Following this, a cautious institution of arsenical therapy in small doses may be tried. If the patient stands this therapy without any untoward effects, the practice in the clinics consists in the administration of alternate courses of an arsenical and a heavy metal. The extent to which this type of therapy should be carried out depends on the

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<sup>15</sup> Stokes, J. H., and others. Standard Treatment Procedure in Early Syphilis, *Ven Dis Inform* **15** 149 (April) 1934, *J A M A* **102** 1267 (April 21) 1934



patient's condition at the time he is first seen and on his reaction to treatment. Rest may be an absolute indication for a time, and restriction of physical activity for a period may be required. Decompen-sation must be avoided at all costs. Naturally, even after specific therapy is discontinued, such a patient should be kept under close observation throughout life.

*Severe Reactions Resulting from Arsenical Treatment*—The 326 patients with uncomplicated syphilitic aortitis received a total of 5,313 arsenical injections. Twelve showed a severe reaction, or a rate of 2.25 per thousand injections. The reactions consisted of crustaceous dermatitis in 4 patients, icterus in 4, ocular damage in 3, and purpura haemorrhagica in 1. Crustaceous dermatitis resulted from the use of neoarsphenamine in 2 cases and from the use of arsphenamine in 2. In three cases icterus resulted from the administration of old arsphenamine, and in 1, from neoarsphenamine. In all 3 cases of ocular damage the condition was due to the administration of tryparsamide employed in the treatment of concomitant syphilis of the central nervous system. Purpura haemorrhagica, which was mild, was due to the administration of sulfarsphenamine.

#### SUMMARY

The frequency of incidence of uncomplicated syphilitic aortitis is 4.9 per cent in patients admitted to the clinic with latent syphilis or syphilis in the late stage (exclusive of benign late syphilis of the bones or skin and syphilis of the viscera other than the cardiovascular organs). The total number of patients with uncomplicated syphilitic aortitis was 326. The manifestation was observed nearly three times more frequently in Negroes than in white patients.

Ten per cent of the patients in whom uncomplicated syphilitic aortitis was detected had had the infection for less than five years.

The Wassermann reaction of the blood was positive in 72 per cent of the cases. There were unquestionable abnormalities of the spinal fluid in 49 per cent of the cases in which examination was made.

Of 935 patients with the early stage of syphilis followed for a period of from three to ten years, cardiovascular syphilis developed in 1.6 per cent, among 105 patients followed for from ten to twenty years, cardiovascular syphilis developed in 6.7 per cent. However, among the patients who were followed from three to twenty years, none of the graver forms of cardiovascular syphilis developed if treatment had been adequate and regular during the early stages of syphilis.

It was noted that treatment definitely improved the outlook in 26.7 per cent of patients followed for one year or more after the detection of uncomplicated syphilitic aortitis.

The average duration of life in patients who died had been increased from thirty-four to eighty-five months when adequate treatment had been given after the detection of uncomplicated syphilitic aortitis

Of patients adequately treated after the detection of uncomplicated syphilitic aortitis, 63 per cent were living and free from symptoms, with no progression of the cardiovascular syphilis, as compared with 49 per cent of those inadequately treated

Cardiovascular syphilis was definitely or probably the cause of death in 79 per cent of the patients inadequately treated after the detection of uncomplicated syphilitic aortitis, as compared with 24 per cent of those adequately treated

The average duration of life for patients who had been treated with small doses of arsenicals was twenty months longer than that for patients who had been treated with large doses

In cases of uncomplicated syphilitic aortitis it is well to give a preliminary course of injections of a soluble or an insoluble preparation of heavy metal

# COOPERATIVE CLINICAL STUDIES IN THE TREATMENT OF SYPHILIS CARDIOVASCULAR SYPHILIS

## II SYPHILITIC AORTIC REGURGITATION ITS TREATMENT AND OUTCOME

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One of the gravest cardiovascular complications of syphilis is that of aortic regurgitation. A complicating aortitis is always present, occasionally an aneurysm accompanies the picture, and all too often there is secondary myocarditis or congestive heart failure. The tendency in the United States seems to be to put even a graver prognosis on this disease than is done in England. Scott<sup>1</sup> estimated the duration of life for patients with untreated aortic regurgitation at from one to two years from the onset of symptoms. On the other hand, Moore and his co-workers,<sup>2</sup> in their recent report of statistics, gave the average duration of life from the onset of symptoms to death or the last observation as thirty months with little or no treatment administered, while the time was increased to sixty-four months with adequate treatment of more than one year. In the first paper of this series on cardiovascular syphilis, observations on uncomplicated syphilitic aortitis from the standpoint of symptomatology and outcome following treatment have been

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The names with an asterisk represent members of the United States Public Health Service, those without an asterisk represent members of the Cooperative Clinical Group.

From the syphilis clinics of the Western Reserve University, the Johns Hopkins University, the Mayo Clinic, the University of Pennsylvania and the University of Michigan, assisted by the United States Public Health Service, with the financial support of an anonymous donor.

1 Scott, R W. Syphilitic Aortic Insufficiency, Arch Int Med **34** 645 (Nov) 1924

2 Moore, J E, Danglade, J H, and Reisinger, J C. Treatment of Cardiovascular Syphilis, Arch Int Med **49** 879 (June) 1932

reported by us as the Cooperative Clinical Group. The present paper deals with the group's material on aortic regurgitation. An analysis of the symptoms, physical signs, roentgenologic findings and electrocardiographic observations in cases of syphilitic aortic regurgitation has been omitted purposely. The discussion is confined to the results obtained with modern antisyphilitic therapy.

#### MATERIAL

Among 6,253 patients admitted to the clinics with syphilis in a late stage<sup>3</sup> or with latent syphilis who were treated or observed for a period of six months or longer, there were 619 who manifested on admission or subsequently showed some form of cardiovascular syphilis, 257 of whom, or 41 per cent of the 6,253 patients, had aortic regurgitation<sup>4</sup>. Three additional patients came into the clinic and subsequently showed aortic regurgitation, making a total of 260 patients with this symptom in the entire group of patients with cardiovascular syphilis<sup>5</sup>.

*Influence of Observations and Sex*—The group of 257 patients with aortic regurgitation consisted of 173, or 34 per cent, of 5,089 white patients and 84, or 72 per cent, of 1,164 Negroes admitted to the five cooperating clinics with latent syphilis or syphilis in a late stage (principally involvement of the cardiovascular and central nervous system). Thus, aortic regurgitation was observed twice as frequently in Negro as in white patients. It was found that among the males the difference was even more marked, as 37 per cent of the male patients were white and 121 per cent, or over three times as many, were Negro. In females the incidence was 26 per cent in white patients and 38 per cent in Negroes. The frequency was higher in males than in females, being 47 and 29 per cent, respectively. The fact that a Negro engages in more strenuous physical labor than does a white man undoubtedly influences to some extent the relatively higher frequency of cardiovascular syphilis in the Negro.

*Duration of Infection on Detection of Syphilitic Aortic Regurgitation*—Among the total of 260 patients with aortic regurgitation, there

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3 The cases of syphilis in the late stage are exclusive of those of benign involvement of bone or the skin or those of syphilis of the upper respiratory tract, eyes, glands or the viscera other than cardiovascular involvement. Therefore, the percentage represents only the relative frequency of cardiovascular syphilis in the population groups considered.

4 The criteria for the diagnosis of aortic regurgitation and aneurysm used by this group are in accord with those established by Carter and Baker (Bull Johns Hopkins Hosp 48 315, 1931).

5 In the five cooperating clinics a total of 642 patients with cardiovascular involvement had been under treatment for at least six months. There were also 349 additional patients with cardiovascular syphilis who were seen for less than six months and whose cases are not included in our analysis. Of the 349 patients, the condition in 145 was diagnosed as aortic regurgitation and of these 40 per cent died before six months had elapsed.

were 142, or 55 per cent, in whom the duration of the infection was known. It is interesting that in 3 cases the condition developed within five years of infection. Aortic regurgitation was observed most frequently in the period from twenty to thirty years after infection.

*Serologic Findings in the Blood and Spinal Fluid*—When serologic tests of the blood were made within ten days of the detection of the aortic regurgitation the results in 85 per cent of the cases showed some degree of positivity. This high percentage of positive Wassermann tests is in contrast to the 72 per cent noted in the cases of uncomplicated syphilitic aortitis.

Lumbar punctures were made on 133 of the 260 patients, the spinal fluid showed a definite abnormality in 62 per cent. This percentage is higher than that noted in our preceding study of uncomplicated syphilitic aortitis (49 per cent).

*Concomitant Syphilitic Involvement of Systems Other Than the Cardiovascular System*—It is well known that frequently in cases of cardiovascular syphilis there is concomitant involvement of the central nervous system. Forty-four per cent of the patients with aortic regurgitation had coexisting syphilis of the central nervous system, either asymptomatic or symptomatic. A similar condition was noted among the patients with uncomplicated syphilitic aortitis. It probably would be well to state that the 62 per cent with positive reactions of the spinal fluid, mentioned in the preceding paragraph, represented only 82 patients. No doubt the puncture was carried out principally when there was some clinical evidence of syphilis of the central nervous system. In the group of 260 patients with aortic regurgitation, 114, or 44 per cent, showed either clinical or laboratory evidence of syphilis of the central nervous system.

*Treatment Prior to Detection of Aortic Regurgitation*—Among the 260 patients, 178, or 69 per cent, had had no treatment or only a little heavy metal, and an additional 13, or 5 per cent, gave a history of an unknown amount of arsenical treatment. One may well raise the question: Why is it that aortic regurgitation is not noted more frequently in patients who have had treatment? The therapy must be a factor in the presence or absence of the disease.

Of the 82 patients who had received therapy prior to the detection of aortic regurgitation, 50 had had less than thirteen arsenical injections, with an interim course of a heavy metal, and of the 32 patients who had received thirteen or more arsenical injections, with an interim course of a heavy metal, only 19 had received this treatment prior to the appearance of cardiovascular syphilis.

*Outcome of Treatment of Syphilitic Aortic Regurgitation*—In determining the end-results of treatment, the cases of patients who

had been under observation or treatment for a period of less than one year were excluded from the study. This action was taken to meet the possible criticism that the person who received much treatment did so because his physical condition on beginning treatment was better and therefore the prolongation of life was more dependent on this factor than on the efficacy of the indicated amounts of treatment. After this exclusion was done, it was found that proportionately the number of patients who died and those still living had had an equal opportunity for treatment.

Treatment after the detection of syphilitic aortic regurgitation was considered under four groupings: (1) an inadequate amount of arsphenamine and a heavy metal, (2) an inadequate amount of arsphenamine and an adequate amount of a heavy metal, (3) an adequate amount

TABLE 1—*Effectiveness of Treatment After Detection of Aortic Regurgitation in the Prolongation of Life\**

Amount of Treatment After Detection of Aortic Regurgitation†		Patients				Average Duration of Life After Detection of Aortic Regurgitation, Months		
Arsenical	Heavy Metal	Living		Dead, All Causes		Living	Dead	Total
		Number	Percentage	Number	Percentage			
Little	Little	39	72.2	15	27.8	41	38	40
Little	Much	34	68.0	16	32.0	47	45	46
Much	Little	9	64.3	5	35.7	40	39	40
Much	Much	59	80.8	14	19.2	56	53	55
Total		141	73.8	50	26.2	49	44	47

\* This and the following tables include only the cases of patients who were under treatment or observation for one year or more.

† Little for arsenical injections means less than thirteen (inadequate), and much means thirteen or more (adequate). Little for a heavy metal means less than twenty injections or weeks of rubs (inadequate), and much means twenty or more (adequate).

of arsphenamine and an inadequate amount of a heavy metal, and (4) an adequate amount of both drugs. Less than thirteen injections of arsphenamine and less than twenty injections of a heavy metal were considered inadequate, more than these amounts was adequate.

In table 1 the cases of 191 patients who had been under observation or treatment for a period of one year or longer are listed, both for those who are living and for those who died, in terms of the amount of treatment administered after the detection of aortic regurgitation and the average prolongation of life effected through the administration of treatment. As the prolongation of life through treatment for the living and that for the dead patients is similar, and as the highest proportion of those still living had received adequate amounts of arsphenamine and a heavy metal, the effectiveness of treatment has been evaluated on the basis of the total number of patients rather than on the small number who died.

When inadequate amounts of arsphenamine and a heavy metal were administered after the detection of aortic regurgitation, there was an average duration of life of forty months, which period increased to fifty-five months when adequate treatment was administered. Since this difference is statistically significant and since precautions have been taken to eliminate the cases of patients who remained under treatment or observation for an insufficient length of time, it appears from the limited material studied that adequate treatment after the detection of aortic regurgitation definitely prolongs life.

An interesting observation of the effectiveness of a heavy metal in treatment was made through the comparison of the condition of the patients who received an adequate amount of both drugs with the condition of those who received an adequate amount of arsphenamine and an inadequate amount of heavy metal. An increase from forty to fifty-

TABLE 2—*Outcome in Cases of Aneurysm and Aortic Regurgitation in Which There Was Congestive Heart Failure Before Beginning Treatment\**

Congestive Heart Failure Before Treatment	Total Number of Cases		Living		Dead, All Causes		Average Duration of Life from Onset of Cardiovascular Syphilis to	
	Num ber	Per cent age	Num ber	Per cent age	Num ber	Per cent age	Last Ob- servation on Living Patient	Death
Present	50	100.0	29	58.0	21	42.0	33 mo	30 mo
Absent	231	100.0	175	75.8	56	24.2	45 mo	47 mo
Total	281*	100.0	204	72.6	77	27.4	43 mo	42 mo

\* This is exclusive of 26 cases in which data relative to the presence or absence of congestive heart failure before treatment were not reported.

five months was noted. These data indicate that an adequate amount of both the heavy metal and the arsenical is highly desirable in the treatment of this grave form of cardiovascular syphilis.

*The Factor of Congestive Heart Failure in Cases of Aneurysm and Aortic Regurgitation*—It is well known to the internist and to the cardiologist that congestive heart failure is one of the most important factors which enter into the problem of cardiovascular syphilis, especially aortic regurgitation and aneurysm. In table 2 are given data on a total of 281 cases of aneurysm and aortic regurgitation for which information with regard to the presence or absence of congestive heart failure before treatment was noted. Two hundred and four patients were living and 77 were dead (all causes). Forty-two per cent of the patients in whom congestive heart failure was present died, and the average duration of life was thirty months, when congestive heart failure was not present (24 per cent) about one-half as many died, and the average span of life was increased to forty-seven months. Con-

gestive heart failure in a case of aneurysm or aortic regurgitation therefore adds greatly to the seriousness of the prognosis

Congestive heart failure was found to increase the gravity of the prognosis of aortic regurgitation or aneurysm, regardless of whether it occurred before, during or after treatment (table 3) Of the patients in whom it was present, 33 per cent died as a result of the syphilitic cardiovascular condition, an additional 12 per cent died of some other or an unknown cause, whereas in the absence of congestive heart failure only 5 per cent of the patients with aortic regurgitation or aneurysm died of cardiovascular syphilis, and 15 per cent died of some other or unknown cause

It was found that if the patient had had an attack of congestive heart failure he would be more likely to have a recurrence of this complication than if he had never previously experienced an attack Among

TABLE 3—*Outcome in Cases of Cardiovascular Syphilis As Influenced by the Presence of Congestive Heart Failure Before, During and After Treatment*

Outcome	Total Number of Cases		Heart Failure Never Present		Heart Failure Present at Some Time	
	Number	Percentage	Number	Percentage	Number	Percentage
Living	203	73.0	160	80.0	43	55.1
Dead of cardiovascular syphilis	36	13.0	10	5.0	26	33.3
Dead of other or unknown cause	39	14.0	30	15.0	9	11.6
Total	278*	100.0	200	100.0	78	100.0

\* This is exclusive of 29 cases in which data relative to the presence or absence of congestive heart failure were not reported

the 195 living patients who had aortic regurgitation or aneurysm on admission, 30 per cent of those who had had congestive heart failure experienced a second attack, as compared with only 9 per cent of the patients in whom this complication had never occurred Of the 72 patients who died, 89 per cent of those who experienced a previous attack had a recurrence, as contrasted with 25 per cent of patients in whom this condition had been absent

#### *Symptomatic Relief Obtained in Cases of Aortic Regurgitation—*

A patient is recorded as having obtained symptomatic relief if one or more of his severe symptoms has been alleviated, if no other severe symptoms have developed or if the original symptoms have not become worse The patients studied were not limited to those followed for one year or more after the detection of syphilitic aortic regurgitation, since it is believed that symptomatic relief can be experienced in a shorter period Such relief was found by 30 per cent of the patients who had received less than thirteen injections of an arsenical, with an interim course of a heavy metal, while of those who had received thirteen or more injections, relief was obtained by 60 per cent Comparable forms



of medical regimen for the treatment of cardiac disease were followed in all cases, regardless of whether antisyphilitic treatment was administered

*Treatment of Syphilitic Aortic Regurgitation*—It has been mentioned that 69 per cent of the 260 patients with aortic regurgitation had had no treatment, or only a little heavy metal, previous to the diagnosis. Moreover, among the other 31 per cent, the treatment had been irregularly administered during many years, with long lapses and generally with little arsenical medication, or else with treatment given after the patient showed syphilitic cardiovascular involvement. The physician should prevent aortic regurgitation by thorough, continuous treatment of syphilis in the early stage, giving adequate and regular treatment of at least from twenty to thirty injections of an arsenical and an appropriate amount of a heavy metal, preferably bismuth, as outlined in "Standard Treatment Procedure in Early Syphilis" <sup>6</sup>

If aortic regurgitation is already established the physician must govern his procedure by the condition of the heart. If the patient shows exertional dyspnea or cyanosis he should be placed in bed for a period of a month or more and careful treatment of the syphilis should be instituted. All risks of reaction to treatment, even a severe gastric upset, must be avoided. An intramuscular injection of either a water-soluble preparation of bismuth or a mercury compound may be given every other day, or an injection of an insoluble salt weekly, for a period of from eight to ten weeks, administering potassium iodide by mouth at the same time. If the patient seems to respond to this treatment, it may then be possible to start arsenical therapy very cautiously in the form of neoarsphenamine, to avoid a therapeutic paradox or a Herxheimer reaction. Arsphenamine is probably too strong in such cases, at any rate in the beginning. At the first sign of intolerance or decompensation arsenical therapy should be stopped. The first dose of neoarsphenamine should be 0.05 Gm., and the dose should be gradually increased to from 0.3 to 0.45 Gm. maximum, with injections weekly for a course of twelve doses. This course of an arsenical may then be followed with from ten to twelve weekly injections of an insoluble bismuth salt, such as bismuth salicylate, or of a water-soluble salt suspended in oil, e. g., sodium potassium bismuth tartrate, 0.1 Gm., or of a liposoluble preparation. Moore, Danglade and Reisinger <sup>2</sup> in such a case advised against routine lumbar puncture unless there is outspoken clinical evidence of neurosyphilis. The cardiovascular condition is more important than asymptomatic neurosyphilis. If the patient stands treat-

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<sup>6</sup> Stokes, J. H., and others. Standard Treatment Procedure in Early Syphilis. *Resumé of Modern Principles, Ven. Dis. Inform.* **15**: 149 (April) 1934, *J. A. M. A.* **102**: 1267 (April 21) 1934.

ment well, alternating courses of neoarsphenamine and bismuth may be continued for some time. Naturally, such a patient must be kept under close observation, as there is danger at all times of a cardiac breakdown. His activity must be restricted, and with the evidence of cardiac failure suitable measures are indicated. Certain patients are unable to tolerate any arsenicals, and the attending physician is forced to depend on injections of bismuth or injections of mercury and potassium iodide. There is some difference of opinion on the value of arsenicals for a patient with anginoid symptoms. Certainly the arsenicals must be used with exceptional caution. However, in a small series of 24 patients with anginoid symptoms on admission, the best results were obtained with thirteen or more injections of an arsenical, with an interim course of a heavy metal.

Reference has been made to the frequent concomitant involvement of syphilis of the central nervous system with cardiovascular syphilis. It is possible that the cardiovascular syphilis may be more or less obscured at the first examination. In this instance, if the physician immediately institutes arsenical treatment for syphilis of the central nervous system, there is the possibility that either therapeutic shock or a cardiac therapeutic paradox, such as that described by Wile,<sup>7</sup> may result. Because of this possibility, it is recommended that all patients with latent and tertiary syphilis, especially those with syphilis of the central nervous system, be examined carefully from the standpoint of cardiac involvement. Moreover, one may well begin therapy with a heavy metal and with potassium iodide if there is the least suspicion of a cardiovascular syphilitic complication.

#### SUMMARY

There were 260 cases of syphilitic aortic regurgitation in the entire group of cases of cardiovascular syphilis. Two hundred and fifty-seven patients were admitted with latent syphilis or syphilis in the late stage (principally with involvement of the cardiovascular or the central nervous system), and an additional 3 patients admitted with syphilis in the early stage were detected during treatment in these clinics.

The frequency of aortic regurgitation in patients who had been under observation or treatment for six months or longer and who were admitted with syphilis in the late stage (principally with involvement of the cardiovascular or central nervous system) or with latent syphilis was 4.1 per cent.

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<sup>7</sup> Wile, U. J. Treatment of Syphilitic Liver and Heart, *Am. J. M. Sc.* **164** 415, 1922, Principles Underlying Treatment of Cardiovascular Syphilis, *Am. Heart J.* **6** 157 (Oct.) 1930.

Aortic regurgitation was observed twice as frequently in the Negro as in the white patients, the incidence was more than three times higher in Negro men than in white men

Aortic regurgitation was observed most frequently from twenty to thirty years after infection

The Wassermann reaction of the blood showed some degree of positivity in 85 per cent of the cases in which the test was carried out within ten days of the detection of aortic regurgitation

In the cases in which a lumbar puncture was done, the spinal fluid of 82, or 62 per cent, showed definite abnormalities

One of the most interesting facts revealed from these data is that 69 per cent of the patients had had no antisyphilitic treatment prior to that given for aortic regurgitation

The treatment administered to certain patients who apparently received adequate therapy before the appearance of the aortic regurgitation was found to have been irregularly given after the syphilis was in the late stages

The average duration of life was increased from forty to fifty-five months with adequate treatment after the detection of the syphilitic aortic regurgitation

The administration of an adequate amount of both an arsenical and a heavy metal was found to be highly beneficial to patients with syphilitic aortic regurgitation

For the patients with syphilitic aortic regurgitation or aneurysm who died, the average duration of life was thirty months when congestive heart failure was present before treatment and forty-seven months when congestive heart failure was not present

Cardiovascular syphilis was the cause of death in 33 per cent of the patients in whom congestive heart failure had been present at some time and in 5 per cent of those in whom it had never been present

Symptomatic relief was noted in 30 per cent of the patients who had received less than thirteen injections of an arsenical, with an interim course of a heavy metal, and in 60 per cent of the patients who had received thirteen or more injections of an arsenical, with an interim course of a heavy metal

A scheme of treatment for use in cases of aortic regurgitation is given

# COOPERATIVE CLINICAL STUDIES IN THE TREATMENT OF SYPHILIS CARDIOVASCULAR SYPHILIS

## III ANEURYSM ITS SYMPTOMATOLOGY, DIAGNOSIS, TREATMENT AND OUTCOME

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The use of the term aneurysm in this paper is confined to a sacculated pocket of an artery due to fibrosis and destruction of the elastic tissue of the wall of the vessel from specific inflammation of the vasa vasorum. In some cases there may be associated mediastinitis and perivasculitis. Fusiform dilatation of the aorta, or of another large artery, is not included under the heading of aneurysm, though we agree with Grant<sup>1</sup> that it may sometimes be difficult to make the clinical distinction between fusiform and saccular dilatation. Although the fundamental pathologic processes of fusiform and saccular aneurysms are identical, the clinical manifestations, prognosis and amenability to treatment of the two conditions make it advisable to consider them separately. A paper dealing with the fusiform aneurysm and comparing the end-results of treatment in cases of that condition with those obtained in cases of saccular aneurysm will appear at a later date. However, in the present series the data on 27 cases of fusiform aneurysm have been evaluated as a part of those on the group of cases of uncomplicated syphilitic aortitis.

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The names with an asterisk represent members of the staff of the United States Public Health Service, those without an asterisk represent members of the Cooperative Clinical Group.

From the syphilis clinics of the Western Reserve University, the Johns Hopkins University, the Mayo Clinic, the University of Pennsylvania and the University of Michigan, assisted by the United States Public Health Service, with the financial support of an anonymous donor.

1 Grant, R T. After Histories for Ten Years of One Thousand Men Suffering from Heart Disease. A Study in Prognosis, Heart 16 275, 1933.

The location and the size of the aneurysms may vary, and a patient may have several aneurysms. It is unnecessary to discuss the pathology of aneurysm. Its specific character is generally accepted.

#### MATERIAL STUDIED

Among the 6,253 patients admitted with syphilis in the late stage<sup>2</sup> or with latent syphilis who were treated or observed for six months or longer in the five cooperating clinics, there were 73, or 12 per cent, who on admission manifested or subsequently had aortitis with saccular aneurysm<sup>3</sup>. In addition to these, there was 1 patient who was admitted to the clinic with syphilis in the early stage who subsequently showed an aneurysm<sup>4</sup>. Among the 73 patients with an aneurysm, 37 were white, and 36 Negro. There were proportionately four times as many Negro patients with a saccular aneurysm as there were white patients. A similar fact has been noted frequently in the medical literature. Aneurysm was found seven times more frequently in Negro males than in white males, while among females this diagnosis was noted in more than twice as many Negro patients as in white patients.

#### OBSERVATIONS

*Duration of Syphilitic Infection at the Time of Detection of Aortitis with Aneurysm*—The time of infection was known in 57 per cent of the 74 cases of aneurysm, and in 50 per cent of these the aneurysm was detected in the period from fifteen to twenty-five years after infection. Three cases of aneurysm were disclosed as late as from thirty-five to forty years after infection.

*Location of Aneurysm*—The greater number of aneurysms involved the arch of the aorta (in 21 of the total of 74 cases). In 19 cases the aneurysm involved the descending portion of the aorta, in 8, the ascending portion, in 4, the abdominal portion, in 4, the arch and the descending portion, in 3, the arch and the ascending portion, in 2, the thoracic portion, in 1, the subclavian artery, in 1, the carotid artery, in 1, the ascending and the descending portion of the aorta, in 1, the descending portion and the carotid artery, in 1, the ascending portion and the innominate artery, in 1, the innominate artery, in 1, the arch of the

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2 The cases of syphilis in the late stage do not include those with a benign involvement of bone or the skin or those of syphilis of the respiratory tract, glands or viscera other than of the cardiovascular system. Therefore, the figures represent simply the relative frequency of these manifestations in the race and sex population considered.

3 The criteria for the diagnosis of aortic regurgitation and aneurysm used by this group are in accord with those established by Carter and Baker (Bull Johns Hopkins Hosp 48 315, 1931).

4 The material for these studies on cardiovascular syphilis comprises 642 cases observed for six months or longer. There were 349 additional cases that were observed for less than six months, and in 101 of these aneurysm was present. In 32 per cent of them the patient died within six months of his admission to the clinic with an aneurysm.

aorta and the subclavian artery, in 1, the subclavian and the innominate artery, in 1, the arch of the aorta and the carotid artery, and in 1, the arch of the aorta and the innominate artery. In 3 instances multiple aneurysms were noted in the following locations: in the arch and in the descending and the abdominal portion of the aorta, in the arch and in the descending portion of the aorta and the innominate artery and in the arch and in the ascending and the abdominal portion of the aorta. Of the 74 patients, 48 are still living and 26 are dead. In 1 instance there was erosion of the vertebra of the thoracic portion of the spine in connection with an aneurysm of the arch of the aorta.

*Serologic Findings in the Blood and Spinal Fluid*—Serologic tests were made repeatedly in most of the cases under observation. Of the 74 cases of aneurysm, a serologic examination of the blood had been made in 51 within ten days of the detection of the aneurysm, the Wassermann reaction was positive in 90 per cent of the cases. Adequate treatment subsequent to the detection of the aneurysm reversed or reduced the positivity of the Wassermann reaction of the blood in 50 per cent of the cases, as contrasted with a change in the reaction in 32 per cent of the cases when an inadequate amount of treatment was given. In 22 of the 74 cases of aneurysm a lumbar puncture was done within two months of the detection of the aortitis with aneurysm. In 64 per cent of these cases there was a frankly positive reaction of the spinal fluid. The examination of the spinal fluid consisted of a Wassermann test, a test for globulin, a colloidal gold test and a cell count.

*Concomitant Syphilis of the Central Nervous System*—Concomitant syphilis of the central nervous system was noted less frequently in the cases of aortitis with aneurysm than in those of uncomplicated syphilitic aortitis. Proportionately, lumbar puncture was done in 29 per cent more cases of uncomplicated syphilitic aortitis than of aortitis with aneurysm. This fact, in part, explains the reduced percentage of incidence of concomitant syphilis of the central nervous system in the cases of aortitis with aneurysm, which was 31 per cent, as against 45 per cent in the cases of uncomplicated syphilitic aortitis. Further, among the cases of aneurysm nearly all instances of involvement of the central nervous system were parenchymatous. In other words, we were dealing with an older type of syphilis than uncomplicated syphilitic aortitis, in which meningeal, vascular and asymptomatic neurosyphilis were noted more frequently. In 92 per cent of the cases of uncomplicated syphilitic aortitis there was asymptomatic neurosyphilis, whereas in cases of aneurysm it coexisted in 54 per cent of the cases. The only other types of concomitant syphilis noted among the cases of aortitis with aneurysm were osseous involvement, which occurred in 2 patients, and involvement of the skin, which occurred in 1 patient. The main point

of interest is that at least 31 per cent of the patients with aneurysm had syphilis of the central nervous system as well, and undoubtedly this percentage would have been higher had a lumbar puncture been done in more patients

*Treatment Prior to Detection of Aortitis with Aneurysm*—Among 74 patients with aneurysm, 77 per cent had had no treatment or only a little heavy metal before the detection of the aneurysm, 7 patients had received eighteen or more injections of an arsenical, with an interim course of a heavy metal, and of these only 2 had received this therapy previous to the detection of cardiovascular syphilis. Apparently the amount of treatment administered to a syphilitic patient, regardless of the stage in which treatment is begun, is important in the prevention of aortitis with aneurysm. A comparison was made with the condition in untreated syphilitic patients to determine if treatment of the syphilis had either a deterring or an accelerating influence on the development of cardiovascular syphilis, but the limited number of cases of a known duration of infection prevented any conclusive statement on this point.

*Symptomatic Relief by Therapy*—A patient is considered to have had symptomatic relief from treatment if one, or more, of the severe symptoms is relieved and if the others have not become aggravated. In the presence of progression of any one, or more, of the severe symptoms, the case is classified under the heading of "no symptomatic relief."

In analyzing the data on symptomatic relief the material was not limited to cases under observation or treatment for one year or more, since such relief may be experienced in a shorter period. Among the 74 patients, 64 had some symptoms recorded on detection of the aneurysm. Symptomatic relief was obtained by 43 per cent of the patients who were not given arsenical therapy as a part of the treatment but who did receive good treatment with heavy metal and potassium iodide, whereas symptomatic relief was noted by 30 per cent of the patients who were given less than thirteen injections of an arsenical and an interim course of a heavy metal, 56 per cent of the patients who were given thirteen or more arsenical injections, with an interim course of a heavy metal, responded symptomatically. In all cases, comparable forms of medical cardiac regimen were used, regardless of whether antisyphilitic treatment was administered.

It is interesting to note that of 74 patients with aneurysm 80 per cent were followed for one year or longer after the detection of the aneurysm, 30 per cent for five years or longer and 16 per cent for eight years or longer.

To determine the extent to which the increased duration of life in patients with this grave manifestation was due to better physical condition on admission rather than to the efficacy of the treatment, several statistical controls were established. First, there were excluded from

the study the patients who either lapsed from treatment or died before the termination of the first year of observation and treatment after the detection of the aneurysm. Then the number of years of observation and treatment for the patients still living and for those who died was determined. Among the group with aneurysm, undoubtedly the patient's physical condition on admission did influence the possibility of an increase in the span of life through treatment to a greater extent than with the other types of cardiovascular syphilis. In the patients with aneurysm, 10 per cent more of those who died than of those who were still living at the termination of the study failed to complete the third year of observation and treatment. However, in the remaining 90 per cent, proportionately the same number of patients who died and those who were living had been followed throughout each of the periods of observation and treatment and therefore had had an equal opportunity to receive benefit from the therapy. The treatment administered after the detection of the aneurysm has been analyzed in four groups: (1) an inadequate amount of both the arsenical and the heavy metal, (2) an inadequate amount of the arsenical and an adequate amount of the heavy metal, (3) an adequate amount of the arsenical and an inadequate amount of the heavy metal and (4) an adequate amount of both drugs. For the arsenicals, thirteen or more injections were considered an adequate amount, and for the heavy metal, twenty or more injections, less than these amounts were considered inadequate.

Since the number of cases of aneurysm is very small, the effectiveness of treatment on the prolongation of life will be discussed for the total group of patients. It is true that the patients who were still living had not completed life, and it is therefore impossible to determine to what extent treatment ultimately would prolong life. However, since 41 per cent of the patients who were still living had already received adequate therapy and since proportionately fewer deaths had occurred in this group, it is reasonable to suppose that the patients who were still living and had received adequate therapy would experience a greater average duration of life than those of the other groups.

As will be seen in the table, the average duration of life after the detection of an aneurysm with the administration of an inadequate amount of each drug was thirty-seven months, which increased to seventy-five months when adequate therapy was given. Further evidence of the effectiveness of adequate therapy is that only 55 per cent of the patients who died after receiving adequate treatment died definitely or presumably of cardiovascular syphilis, in comparison with 64 per cent of those who were inadequately treated. Thirteen of the 22 deaths were definitely or presumably due to cardiovascular syphilis. In 4 cases death was sudden, and in the other 9 death occurred after a more or less prolonged illness.



*Therapeutic Paradox*—The factor of "therapeutic paradox," which also influences the course of an aneurysm, may well be considered at this point. Several clinicians have noted that the type of therapy employed in treating patients with aneurysm has great significance. Instances have been reported of disastrous results following the administration of a large dose of an arsenical or the institution of treatment with an arsenical without preliminary heavy metal therapy. In certain of the cases the reaction may be compared to a Herxheimer reaction, resulting in acute edema in a diseased area in the aortic wall, with immediate mechanical weakening of its structure and rupture within from twenty-four to forty-eight hours after treatment. For this the best designation is therapeutic shock. To a slower form leading to a more gradual change Wile<sup>5</sup> has given the name therapeutic paradox. The patient's symptoms at first seem to improve, but later the process

*Effectiveness of Treatment After Detection of Aneurysm in the Prolongation of Life\**

Amount of Treatment After Detection of Aneurysm†		Patients				Average Duration of Life After Detection of Aneurysm, Months		
Arsenical	Heavy Metal	Living		Dead, All Causes		Living	Dead	Total
		Number	Percentage	Number	Percentage			
Little	Little	11	52.4	10	47.6	34	40	37
Little	Much	9	90.0	1	10.0	42	15	39
Much	Little	2	50.0	2	50.0	24	31	27
Much	Much	15	62.5	9	37.5	85	58	75
Total		37	62.7	22	37.3	56	45	52

\* This group includes only cases in which the patient was under treatment or observation for one year or more.

† Little for arsenical injections means less than thirteen (inadequate), and much means thirteen or more (adequate). Little for a heavy metal means less than twenty injections or weeks of rubs (inadequate), and much means twenty or more (adequate).

may become aggravated. This is due presumably to a too rapid healing of the inflammatory area in the wall of the vessel, resulting in fibrosis, distortion and contraction.

#### TREATMENT OF SACCULATED ANEURYSM

The limited promise of relief and prolongation of life for a patient with an aneurysm emphasizes the greater need for its prevention. Of the 105 patients who were treated for syphilis in the early stage and were followed up for from ten to twenty years thereafter, only 1 had aortitis with aneurysm, although there is a possibility of its occurrence in other patients as the period of observation is extended. Adequate regular treatment of syphilis in the early stages apparently assures free-

<sup>5</sup> Wile, U. J. Treatment of Syphilitic Liver and Heart, *Am J M Sc* **164** 415, 1922, Principles Underlying Treatment of Cardiovascular Syphilis, *Am Heart J* **6** 157 (Oct) 1930.

dom from this manifestation. As has already been mentioned in this paper, 77 per cent of the patients with aneurysms had had no previous treatment, unless perhaps a small amount of heavy metal, of the 23 per cent who had received some treatment, only 7 had anything approaching adequate modern therapy. In each of these cases treatment had not been given until the late stage of the infection had been reached, in fact, only 2 of the 7 patients had received adequate therapy before the development of uncomplicated syphilitic aortitis. The best therapy for the prevention of aneurysm is continuous treatment of syphilis in the early stage, with from twenty to thirty injections of an arsenical and an interim course of a heavy metal, as outlined in the Cooperative Clinical Group's report, "Standardization of Treatment in Early Syphilis" <sup>6</sup>

With the diagnosis of aneurysm established, the physician must be governed by the conditions found. If there is evidence of decompensation, the patient should rest. If there is an accompanying edema, it may be well to employ a heavy metal diuretic, like salyrgan or merbaphen, though we question the specific action of these preparations. After all, such soluble mercurial compounds as mercury succinimide and red mercuric iodide have a definite diuretic action, the same is also true of certain water-soluble bismuth salts.

As far as specific therapy is concerned, the physician should exercise every care to prevent both the therapeutic paradox and the Herxheimer reaction. Treatment should be started cautiously, with a heavy metal (bismuth or mercury) in the form of either a water-soluble or an insoluble salt, for a period of from eight to ten weeks. Potassium iodide may accompany this therapy. Then arsenical therapy may be started very cautiously, with either neoarsphenamine or an arsenical preparation for intramuscular use. The maximum dose of neoarsphenamine should not be more than 0.3 Gm, possibly starting with a dose of 0.025 or 0.05 Gm. Neoarsphenamine is usually employed in a course of from ten to twelve injections. Alternating between the succeeding courses of neoarsphenamine one may employ an insoluble bismuth salt, such as bismuth salicylate, 0.1 Gm, or a soluble salt suspended in oil, e.g., potassium sodium bismuth tartrate or potassium bismuth tartrate, 0.1 Gm, or a liposoluble salt. Throughout, all strenuous exercise and all reactions to treatment must be avoided. Thereafter, much will depend on the symptoms and on the response to treatment. Naturally a patient with such a condition should be followed and examined physically and roentgenographically every six months or every year throughout life.

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<sup>6</sup> Stokes, J. H., and others. Standard Treatment Procedure in Early Syphilis, Resumé of Modern Principles, Ven. Dis. Inform. **15**: 149 (April) 1934, J. A. M. A. **102**: 1267 (April 21) 1934.

## SUMMARY

Seventy-four cases of sacculated aneurysm were included in the study

In 50 per cent of the cases a saccular aneurysm was observed in the period from fifteen to twenty-five years after the infection, and in 3 cases, as late as from thirty-five to forty years after infection

The location of the aneurysm is given in the text Three patients had three aneurysms each

The Wassermann reaction of the blood was positive in 90 per cent of the cases in which it was made within ten days of the diagnosis, and in 64 per cent of the cases in which lumbar puncture was made within two months of the diagnosis there was a definitely abnormal fluid

Of the total number of patients with aneurysm, 31 per cent showed concomitant involvement of the central nervous system, principally of the parenchymatous type This percentage represents the minimum, since in a number of cases the gravity of the cardiovascular syphilis precluded the making of a lumbar puncture

Seventy-seven per cent of the patients had not been treated prior to the detection of the aneurysm

Of a group of 64 patients with aneurysms, with symptoms on admission, symptomatic relief was obtained in 44 per cent Symptomatic relief was obtained in 43 per cent of the patients who were not given arsenical therapy as a part of the treatment but who did receive a good course of a heavy metal and potassium iodide, whereas symptomatic relief was gained in 30 per cent of the patients who were given less than thirteen arsenical injections and an interim course of a heavy metal, 56 per cent of the patients who were given thirteen or more arsenical injections, with an interim course of a heavy metal, responded symptomatically In all cases comparable forms of medical cardiac regimen were used, regardless of whether antisyphilitic treatment was administered

Of the 74 patients with a saccular aneurysm, 80 per cent were followed for a period of one year or longer after the detection of this involvement, 30 per cent for five years or longer and 16 per cent for eight years or longer

The average duration of life after the detection of the aneurysm of patients receiving an adequate amount of each drug was thirty-seven months, which increased to seventy-five months when adequate anti-syphilitic treatment was given

Among the 22 patients who died, there were 13 who died definitely or presumably of cardiovascular syphilis

An outline of treatment for patients with aneurysm is suggested

# MECHANISM OF ACUTE EXPERIMENTAL HEART FAILURE

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In several previous papers<sup>1</sup> we have reported studies on the cardiac output of patients with congestive heart failure. Such persons usually have subnormal values for the circulatory minute volume, but no correlation between the amount of blood pumped by the heart and the clinical state of the patient was observed. It was noted that a disappearance of congestive phenomena might be associated with an increase, a decrease or no change in the cardiac output. These observations have led to the conclusion that the theory of forward failure does not offer an adequate explanation for the mechanism of congestive heart failure.

Our previous studies have not been directly concerned with the relation of the congestive syndrome to back pressure. However, as has been pointed out,<sup>1a</sup> the observations reported are compatible with this idea as originally expressed by Hope.<sup>2</sup> One of the chief points of the back pressure theory is that failure of only one side of the heart may occur. That this is actually the case has recently been demonstrated by Weiss and Robb,<sup>3</sup> who, using the method of injection of Hamilton,

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From the Department of Medicine, Vanderbilt University

1 (a) Harrison, T R, Friedman, B, Clark, G, and Resnik, H. The Cardiac Output in Relation to Cardiac Failure, *Arch Int Med* **54** 239 (Aug) 1934. (b) Friedman, B, Clark, G, Resnik, H, Jr, and Harrison, T R. Effect of Digitalis on the Cardiac Output of Persons with Congestive Heart Failure, *ibid* **56** 710 (Oct) 1935. (c) Friedman, B, Resnik, H, Jr, Calhoun, J A, and Harrison, T R. Effect of Diuretics on the Cardiac Output of Patients with Congestive Heart Failure, *ibid* **56** 341 (Aug) 1935. (d) Resnik, H, Jr, Friedman, B, and Harrison, T R. The Effect of Certain Therapeutic Measures on the Cardiac Output of Patients with Congestive Heart Failure, *ibid* **56** 891 (Nov) 1935.

2 Hope, James. *Diseases of the Heart and Great Vessels*, Philadelphia, Lea & Blanchard, 1842, p 250.

3 Weiss, S, and Robb, G P. Cardiac Asthma (Paroxysmal Cardiac Dyspnea) and Syndrome of Left Ventricular Failure, *J A M A* **100** 1841 (June 10) 1933.

Moore, Kinsman and Spurling,<sup>4</sup> demonstrated that during paroxysms of cardiac asthma there is a sudden increase in the amount of blood in the lungs. Since this change was noted to be independent of significant alterations in the cardiac output, it appears that cardiac asthma is brought about by back pressure from sudden failure of the left ventricle. The occurrence of unilateral failure of the ventricles appears, therefore, to have been demonstrated.

Another problem concerning the mechanism of heart failure is that of the analogy between congestive failure in man and fatigue of the heart as observed in the heart-lung preparation. Because of the artificial conditions which exist in a heart-lung preparation, many clinicians have been unwilling to grant that conclusions arrived at by this technique are applicable to congestive heart failure as observed in patients. In this regard the recent studies of Starr, Collins and Wood<sup>5</sup> are of interest. These authors studied a large group of subjects without cardiac disease and compared the results with those noted in persons "threatened with heart failure." The difference between the groups was found to consist not so much in the cardiac output—although in general they noted, as did we, that persons with cardiac disease tend to have subnormal values for this function—but rather in an abnormal relationship between the work performed by the heart and its size. The characteristic abnormality in their subjects with impending heart failure was an increase in the size of the heart in proportion to the work done by it. Starr and his colleagues interpreted their observations as meaning that Starling's law of the heart was applicable to man and that heart failure in patients, like that in the heart-lung preparation, was chiefly manifested by an increasing disproportion between the size of a given heart and the work it performed. These conclusions are of special interest when it is remembered that one hundred years ago James Hope emphasized the fact that dilatation was the essential physiologic change responsible for back pressure.

The purpose of the study to be reported in the present paper was to investigate further, under controlled experimental conditions, the mechanism of heart failure. For this purpose drugs known to lead to death by causing heart failure were administered to dogs, and the various circulatory functions were studied during the progressive stages of the disturbances so produced.

4 Hamilton, W. F., Moore, J. W., Kinsman, M. M., and Spurling, R. G. Studies on the Circulation. Further Analysis of Injection Method and of Changes in Hemodynamics under Physiological and Pathological Conditions, *Am J Physiol* **99** 534, 1932.

5 Starr, I., Collins, L. H., Jr., and Wood, F. C. Studies of Basal Work and Output of Heart in Clinical Conditions, *J Clin Investigation* **12** 13 1933.

# VENOUS PRESSURE AND CARDIAC OUTPUT IN EXPERIMENTAL HEART FAILURE

Heart failure has been produced either by chloroform or by potassium chloride. The former drug was administered by inhalation in some experiments and intravenously in others. The latter method has been generally preferred because dosage can be better controlled. When chloroform is given slowly to morphinized dogs the arterial pressure declines and edema of the lungs usually develops, but a rise in the systemic venous pressure occurs only as a terminal event, when the animal is practically moribund. At autopsy the heart is noted to be dilated and the lungs are edematous. When potassium chloride is slowly administered intravenously a different sequence of events occurs. The systemic venous pressure rises gradually. The arterial pressure rises or remains at a normal level for a time and declines suddenly as the animal becomes moribund. At autopsy the heart is noted to be dilated, but gross edema of the lungs is not observed.

TABLE 1—*The Effect of Intravenous Injection of Chloroform on the Circulation of Dogs*

Date, 1934	Weight of Dog, Kg	Conditions	Mean Arterial Blood Pressure, Mm Hg	Arterial Oxygen Content, Vol %	Venous Oxygen Content, Vol %	Arteriovenous Oxygen Difference, Vol %	Oxygen Consumption per Minute, Ce	Cardiac Output per Minute, Liters	Venous Pressure, Mm H <sub>2</sub> O	Comment
3/22	13.5	Control	130	17.30	10.77	6.53	98	1.50	22	
		After 1.7 cc chloroform	46	13.81	1.37	12.44	15	0.12	115	Moribund
3/24	22.8	Control	134	19.25	10.65	8.60	96	1.12	12	
		Control	136	20.43	11.86	8.57	95	1.10	0	
		After 0.5 cc chloroform	120	19.37	10.52	8.85	111	1.25	2	
		After 1.0 cc chloroform	114	16.22	9.86	6.36	124	1.95	2	
		After 1.4 cc chloroform	94	13.07	7.98	5.09	96	1.89	27	
		After 2.6 cc chloroform	56	2.42	?	?	?	?	120	Moribund
3/26	14.8	Control	144	17.18	12.10	5.08	130	2.56	—12	
		Control	141	16.94	12.58	4.34	116	2.67	—13	
		After 0.2 cc chloroform	110	15.37	11.98	3.39	83	2.49	—13	
		After 0.9 cc chloroform	68	9.86	8.17	1.69	31	1.84	56	Moribund

Observations on the circulation of dogs to which chloroform or potassium chloride was administered have been made as follows. The femoral vessels were cannulated for measurement of arterial and venous pressure. The consumption of oxygen was determined by collection and analysis of the expired air. Samples of blood obtained from the femoral artery by direct puncture and from the right ventricle by puncture of the chest were analyzed for the content of oxygen in the Van Slyke-Neill manometric apparatus. The cardiac output was calculated from the consumption of oxygen and the arteriovenous oxygen difference.

Results obtained in animals into which chloroform was injected are indicated in table 1. The arterial blood pressure declined slowly in some experiments and suddenly in others. The animal began to expectorate froth, and when this occurred arterial anoxemia developed. Toward the latter stages of the experiment the consumption of oxygen declined markedly. The arteriovenous oxygen difference increased in some instances, but in other experiments the onset of well marked anoxemia was associated with a diminution in this function. The increase in

cardiac output which was observed in one experiment was probably due to anoxemia. In other experiments the output of the heart diminished. A rise in the systemic venous pressure occurred only as a terminal manifestation. The pulmonary venous pressure was not measured, but it probably rose at a relatively early stage of the experiment, because the development of pulmonary edema, as shown by the expectoration of froth and by the presence of arterial anoxemia, preceded the final circulatory collapse. It is assumed that a rise in the pulmonary venous pressure occurred prior to the development of edema of the lungs.

The results of experiments illustrating the effects of potassium chloride are shown in table 2. A rise in the venous pressure occurred at a relatively early stage and preceded the terminal fall in the arterial

TABLE 2—*The Effect of Potassium Chloride on the Circulation of Dogs*

Date, 1934	Weight of Dog, kg	Conditions	Mean Blood Pressure, Mm Hg	Arterial Oxygen Content, Vol %	Venous Oxygen Content, Vol %	Arterio-venous Oxygen Difference, Vol %	Oxygen Consumption per Minute, Ce	Cardiac Output per Minute, Liters	Venous Pressure, Mm H <sub>2</sub> O
4/7	7.5	Control	108	22.40	18.60	3.80	40	1.04	55
		After 1.2 Gm potassium chloride	116	21.98	16.92	5.06	68	1.34	110
		After 1.8 Gm potassium chloride	120	19.08	14.94	4.14	64	1.55	120
4/19	17.3	Control	114	19.82	12.66	7.16	99	1.38	45
		After 4.5 Gm potassium chloride	119	20.62	13.38	7.24	131	1.81	80
		After 6.9 Gm potassium chloride	113	18.97	13.27	5.70	128	2.25	85
		After 7.2 Gm potassium chloride	40	18.27	4.82	13.45	30	0.22	120
		After 7.5 Gm potassium chloride	38	17.72	3.13	14.59	43	0.29	120
		After 7.9 Gm potassium chloride	32	17.25	3.65	13.60	15	0.11	140
5/26	21.0	Control	150	19.72	13.43	6.29	111	1.77	42
		Control	144	19.48	12.58	6.90	102	1.48	34
		After 2.4 Gm potassium chloride	140	18.70	12.22	6.48	132	2.03	42
		After 3.8 Gm potassium chloride	122	18.50	11.73	6.77	131	1.93	55
		After 3.8 Gm potassium chloride	56	17.54	7.98	9.56	54	0.55	100

pressure. An increase in the consumption of oxygen was noted in the early stages of the experiments and was followed by a fall as the animal went into collapse. Significant arterial anoxemia did not usually occur. The arteriovenous oxygen difference increased in some experiments and not in others. The cardiac output per minute tended to rise as the consumption of oxygen rose in the early stages and then underwent extreme decline when circulatory collapse set in.

The experiments illustrate two significant points. In the first place, they show that the heart does not necessarily fail as a whole but that unilateral failure of the ventricles may occur. Congestion and edema of the lungs brought about by chloroform may appear in the absence of systemic congestion. On the other hand, potassium chloride tends to produce failure of the right ventricle, with congestion and a rise in pressure in the systemic veins. Another point brought out by the experiments is that a significant decline in the output of the heart,

whether considered as such or in relation to the metabolism, does not regularly occur during the early stages of heart failure and may be preceded by congestive phenomena either in the systemic or in the pulmonary vascular bed

#### MECHANICAL EFFICIENCY OF THE HEART IN RELATION TO HEART FAILURE

*Method of Determining the Mechanical Efficiency of the Heart without Opening the Chest*—The most characteristic physiologic change associated with cardiac fatigue in the heart-lung preparation is dilatation of the heart and an increase in its expenditure of energy, with a corresponding decline in its efficiency as a mechanical pump. Observations on the mechanical efficiency of the heart have not been made previously in intact animals because of the difficulty in determining the cardiac consumption of oxygen. We have devised a procedure which has made it possible to measure the mechanical efficiency of the heart of a dog subjected to no insult other than the administration of sufficient morphine to keep it quiet and the insertion of arterial and venous cannulas. The work done by the heart is measured by determining the cardiac output and the mean arterial blood pressure by the methods described previously. The expenditure of energy of the heart is calculated from the mechanical equivalent of its consumption of oxygen. The latter function is determined as follows. A modified Morawitz cannula is introduced through the right external jugular vein into the coronary sinus. The blood passing out of the cannula is returned to the general circulation through a second cannula in the left external jugular vein. The rubber tube connecting the two cannulas is interrupted by a glass T-tube, so that the blood stream can be diverted and the blood from the coronary sinus collected for measurement of the volume of outflow and of the oxygen content. The outflow from the coronary sinus is assumed to represent 60 per cent of the blood passing through the heart. The coronary flow and the amount of oxygen in the arterial blood and in the venous blood being known, the oxygen consumption of the heart per unit of time can be calculated. From the caloric value of oxygen and the mechanical equivalent of heat, the energy expended by the heart per minute can be estimated in kilogram-meters. This divided into the work performed per minute gives the mechanical efficiency of the heart in terms of the percentage of the energy expended which is converted into work. In order to avoid inaccurate results, it is necessary that the three samples of blood—from the femoral artery, from the right auricle and from the coronary sinus—be taken simultaneously.

The cannula used and the technic employed for passing it into the coronary sinus need to be discussed in somewhat more detail. The cannula is made of thin brass tubing, with an internal diameter of 4.5 mm and a wall somewhat less than 0.5 mm thick (figs 1 and 2). The cannula should be from 30 to 35 cm long. Three centimeters from the distal end it is bent at an angle of 10 degrees. Two millimeters from the distal end several oval holes 3 by 4 mm are made in the wall so as to allow free entrance of blood in case the open distal end becomes occluded by the sinus. At distances of 1 and 2 cm, respectively, from the distal end are grooves for tying on a rubber balloon, as in the ordinary Morawitz cannula. Between the grooves is a hole 1 mm in diameter, into which is sealed the lower end of a small brass tube, which passes from this point inside the cannula to a point 2 cm from its proximal end and then through the wall. The purpose of this tube is to allow inflation of the balloon with air when the cannula is in



place, so as to hold it in position and to prevent the escape of blood from the coronary sinus except through the cannula. Thus, the cannula is like that described by Morawitz and Zahn,<sup>6</sup> except for its greater length and for the slight bend at the distal end

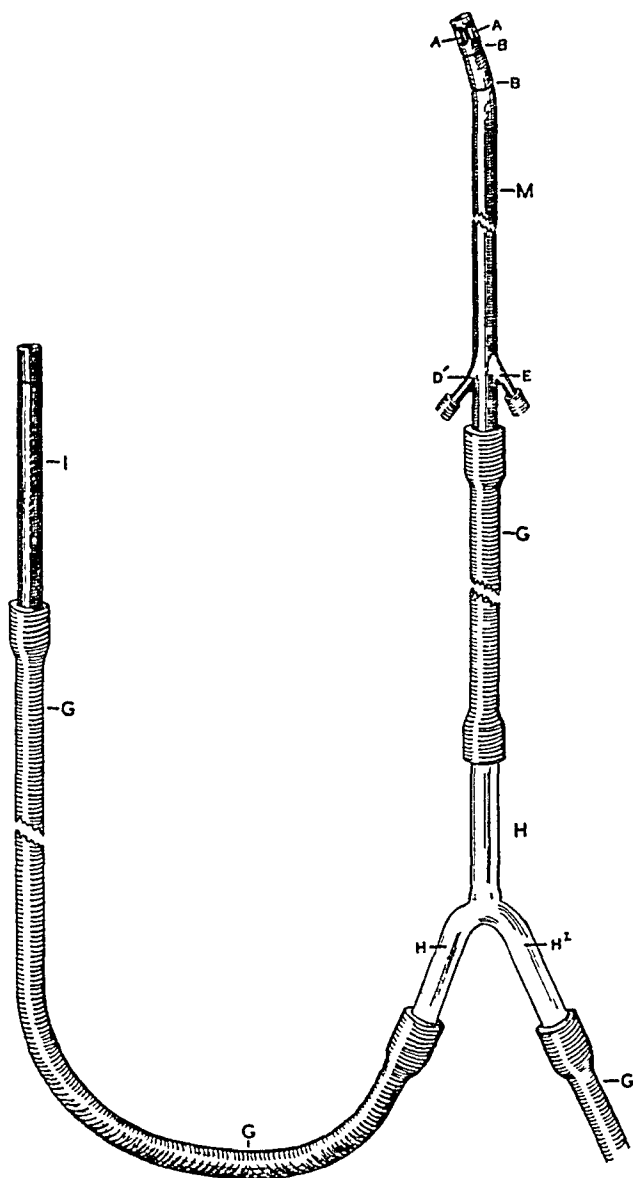


Fig 1—*A* indicates openings in the distal end of the cannula, *B* and *B'*, grooves for tying on the rubber balloon, *M*, the main body of the cannula, *D'*, the proximal end of the small internal brass tube for inflating the balloon, *E'*, the proximal end of the small internal brass tube opening into the auricle, *G*, the rubber tubing, *H*, *H'* and *H*<sup>2</sup>, the glass Y-tube, and *I*, the metal cannula for returning the blood into the left external jugular vein

6 Morawitz, P, and Zahn, A Ueber den Koronarkreislauf am Herzen in Situ, Zentralbl f Physiol **26** 465, 1912

In addition to the small internal brass tube through which the balloon is inflated, we have used a second brass tube, which passes into the wall of the cannula 2 cm from the proximal end and down to a point 3 cm from the distal end, where it terminates as an opening sealed into the wall of the cannula. This tube has offered two advantages. Through it the venous pressure in the right auricle can be measured and samples of mixed venous blood can be obtained. The necessity for puncturing the heart through the chest is thereby obviated.

The proper preparation of the rubber balloon at the distal end of the cannula is of great importance, for if it is not well inflated part of the venous blood may

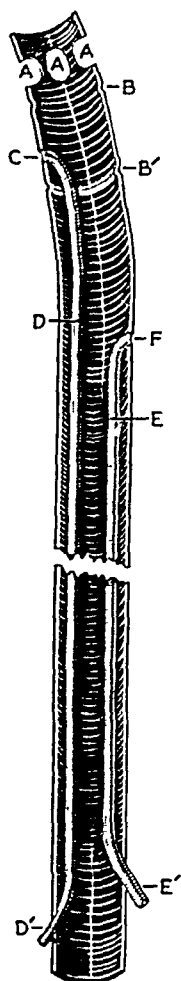


Fig 2—*A* indicates openings in the distal end of the cannula, *B* and *B'*, grooves for tying the balloon, *D-D'*, the small internal brass tube for inflating the balloon, *C*, the distal opening of the tube *D-D'*, *E-E'*, the small internal brass tube for obtaining samples of blood and measuring pressure in the right auricle, and *F*, the distal opening of the tube *E-E'*. This drawing represents a cross-section of the cannula.

escape around the cannula and false results may be obtained for the flow of blood from the coronary sinus. The best results have been obtained with a dental rubber dam, which is tied with fine thread into the two grooves at the distal end of the cannula. The use of small amounts of rubber cement in the grooves has been useful in preventing the balloon from leaking.

The procedure for inserting the cannula into the coronary sinus without opening the chest is as follows. With the dog lying on its back, the two external jugular veins are dissected free in the neck. (In order for the vein to be large enough to admit the cannula freely, dogs weighing from 14 to 20 Kg should be used. With smaller animals serious difficulty is often encountered in introducing the cannula into the vein.) A short metal cannula of the same bore as that of the coronary cannula is inserted into the left jugular vein. The coronary cannula, with the balloon tied on but not inflated, is greased with liquid petrolatum and then passed down into the right jugular vein. After the tip of the cannula is well in the thoracic cavity the distal end should be pointed somewhat upward and to the left. The instrument is steadily pushed until it reaches the tip of the right ventricle. The distance from a fixed point on the dog's chest to the proximal end of the cannula is then measured. This measurement is of importance, for numerous observations have shown that when the distal end is in the coronary sinus the proximal end is from 1 to 2 cm more cephalad than when the distal end is in the tip of the right ventricle. The cannula is withdrawn for a distance of about 4 cm and rotated in such a way that the inclined distal end points downward, i e, toward the dog's back. The proximal end of the cannula is raised somewhat, and the instrument is pushed gently in an axis corresponding to the long axis of the dog's body. If the cannula passes into the inferior vena cava, it can readily be pushed beyond its previous position at the apex of the right ventricle, and it is withdrawn a few centimeters and again gently pushed caudad. After a time the cannula will meet an obstruction, when it is from 1 to 2 cm cephalad of its original position in the ventricle. The cannula is then against the wall of the right ventricle, in the coronary sinus or in a small recess in the auricle lying between the orifices of the sinus and the inferior cava. The rubber tubing from the end of the cannula is removed, and the pulsation and the character of the blood flowing out are noted. If the cannula is in the right ventricle the stream flows freely, the blood is of maroon color and has a forceful systolic pulsation. If the cannula is in the auricular recess there is little or no pulsation except with respiration and the blood flows slowly and is of maroon color. When the cannula is in the sinus there is a distinct, although not forceful, systolic pulsation, with a free outflow, and the blood is almost black. In case of doubt it is necessary to compare the color of samples of blood drawn through the main orifice of the cannula with those obtained through the small upper brass tube which opens into the auricle. The blood passing out of the coronary sinus is much darker than the mixed venous blood from the right side of the heart.

In order that one may be reasonably certain that the tip of the cannula is in the coronary sinus, the following conditions must be fulfilled

- 1 The cannula must come to rest against an obstruction at a point from 1 to 2 cm cephalad to its previous position when passed into the tip of the right ventricle

- 2 The outflowing blood must exhibit distinct systolic pulsations

- 3 The color of the blood passing from the cannula must be distinctly darker than that of the mixed venous blood

- 4 Gentle rotation must fail to dislodge the cannula from its position

When these criteria have been met the balloon should be inflated through the small internal tube with from 0.5 to 1 cc of water, the proximal end of the cannula should be connected with the rubber tubing to the cannula in the left external jugular vein, and the desired observations may be made. At the conclusion of the experiment the animal should be killed, the heart exposed and the

position of the cannula checked after the right auricle is opened Unless the cannula is well within the sinus and unless the balloon is inflated the results of the experiment must be discarded

The most serious of the many difficulties which have been encountered in the experiments has been clotting of the blood In spite of large doses of heparin, clotting has frequently occurred and has spoiled many of the experiments With dogs weighing from 15 to 20 Kg it has been observed that an initial dose of 800 mg of heparin just prior to the introduction of the cannula, followed by doses of 200 mg every half-hour, will usually suffice to prevent clotting for from two to three hours

*Sources of Error in the Calculation of the Efficiency of the Heart*—In the calculation of the consumption of oxygen by the heart it is necessary to make allowance for the fact that all the blood passing into the heart muscle does not flow out of the coronary sinus The question has been studied by Evans and Starling<sup>7</sup> and also by Anrep, Blalock and Hammouda<sup>8</sup> Both reports indicated that approximately 60 per cent of the blood passing through the heart escapes through the coronary sinus and that the proportion varies within relatively narrow limits Our calculations have accordingly been based on the assumption that the measured flow through the coronary sinus represents 60 per cent of the total coronary blood flow It has also been necessary to assume that the utilization of oxygen of the blood from the coronary sinus is similar to that of the blood escaping through the other cardiac venous channels Although both of the assumptions appear probable on the basis of present evidence, it is recognized that they may introduce considerable error into the results

In the calculation of the work done by the heart there are at least three sources of error In the first place, the work of the auricles has been neglected, but since this constitutes a small fraction of the total work, such an omission is probably permissible A more serious source of error is that of neglect of the work done by the heart in imparting velocity to the blood Evans<sup>9</sup> has shown that under conditions of low output the factor of velocity constitutes 5 per cent or less of the total work done but that the magnitude of the fraction increases rapidly as the output rises It is probable that in certain of the experiments to be reported, namely, those in which the effects of increased work were observed, the factor of velocity constituted an important fraction of the total work and that its neglect results in our figures for efficiency being considerably too low On the other hand, in the experiments on acute heart failure, the output of the heart either remained at the same general level or decreased, and we do not believe that the neglect of the factor of velocity is of serious importance

Another source of error in the determination of the cardiac work has been our failure to measure the pulmonary arterial pressure We have arbitrarily assumed this to be one third of the systemic arterial pressure and hence have calculated the work of the right ventricle as being one third that of the left Evans, in his calculations, assumed the pulmonary pressure to be one-sixth the systemic pressure If our assumed value for the pulmonary arterial pressure is 50 per cent in error, this makes a difference of about 15 per cent in the final value for the cardiac work Since our neglect of the factor of velocity tends to make

<sup>7</sup> Evans, C L, and Starling, E H The Part Played by the Lungs in the Oxidative Process of the Body, *J Physiol* **46** 413, 1913

<sup>8</sup> Anrep, C V, Blalock, A, and Hammouda, M N The Distribution of the Blood in the Coronary Blood Vessels, *J Physiol* **67** 87, 1929

<sup>9</sup> Evans, C L Work of the Heart, *J Physiol* **52** 6 1918

the values for the work and for the efficiency too low, we have deliberately chosen a rather high value for the pulmonary arterial pressure, so that any error arising from the latter assumption would tend to have the opposite effect

The assumptions involved and the sources of error concerned in this method for measuring the efficiency of the heart in intact animals have been pointed out in some detail, because they indicate that caution must be exercised in placing too strict a quantitative interpretation on the results obtained. Any attempt to overcome these sources of error would have involved further surgical procedure and would have defeated the purpose of the experiments, which was to measure as accurately as possible the efficiency of the heart in intact animals. The possibility of large errors in any given experiment being granted, the changes to be reported are so great as to be well beyond any likely error involved in the assumptions underlying the calculations.

*The Efficiency of the Heart in Morphinized Dogs*—The data on twenty-three control experiments are given in table 3. The calculated total coronary blood flow was from 52 to 147 cc per minute. Per gram of heart the coronary flow varied from 0.34 to 1.08 cc per minute, the average value being 0.64 cc. The percentage of the total cardiac output passing through the coronary vessels ranged from 29 to 122, the mean value being 57 per cent. The utilization of oxygen of the blood in the heart was very high, varying from 98 to 172 volumes per cent, with an average of 133 volumes per cent. In every animal the utilization of oxygen of the blood passing through the heart was considerably greater than that of the body in general. The values for the systemic arteriovenous oxygen difference ranged between 43 and 105 volumes per cent, with an average of 7 volumes per cent.

In general, about 10 per cent of the total oxygen absorbed was used by the heart, the range of values being from 5 to 23.5 per cent. These values for the cardiac consumption of oxygen are considerably higher than those of Evans, who estimated that the heart used about 4 per cent of the total oxygen absorbed. The difference is probably to be explained by the fact that our dogs had been subjected to no serious surgical procedure and that the hearts were doing considerably more work than was being done in Evans' experiments with heart-lung preparations. The oxygen used by the heart per gram per hour varied between 27 and 93 cc, the average being 53 cc. This value likewise is somewhat higher than that reported by investigators using heart-lung preparations.

The dogs exhibited wide variations in cardiac output, which ranged between 0.89 and 2.9 liters per minute. Per kilogram of body weight the cardiac output ranged between 56 and 173 cc per minute, with an average value of 101 cc. The figures are somewhat less than those reported by Harrison and Blalock<sup>10</sup>. The difference can probably be

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10 Harrison, T. R., and Blalock, A. The Cardiac Output in Pneumonia in the Dog, *J. Clin. Investigation* 2:435, 1926.

TABLE 3—*The Mechanical Efficiency of the Dog's Heart*

Date, 1934	Weight of Dog, Kg	Weight of Heart, per Min, Gm	Coronary		Total Consump- tion of Oxygen per Minute, Cc	Percent age Total Oxygen Used by Heart	General Arterio venous Differ ence, Vol %	Chest Open*	Cardiac Output per Minute, Liters	Mean Arterial Blood Pressure, Mm of Mercury	Total Cardiac Work, per Min Kilo gram meters	Mechanical Efficiency of Heart Cc	Coro nary Flow per Min Gm of Heart, Cc	Percentage Cardiac		Consump tion of Oxygen per Kg of Body Weight, Cc
			Coro nary Flow per Min Cc	Output per Min Cc										Output per Min Cc	Output per Min Cc	
6/20	18.1	154	15.1	4.5	109	10.6	57	1.93	102	372	15.6	0.50	4.0	107	21	60
6/19	15.9	103	13.6	5.3	90	10.1	10.1	0.89	81	140	7.5	0.65	7.5	56	14	57
4/2	20.9	117	12.0	5.1	70	13.8	7.7	0.91	101	175	8.9	0.75	8.8	83	15	64
4/4	21.8	187	13.4	2.7	152	5.0	10.5	1.60	130	397	23.1	0.24	3.9	73	21	70
3/5	19.0	108	15.5	6.9	97	23.5	8.1	1.20	138	284	6.1	0.74	12.2	63	14	51
3/7	12.7	126	15.9	5.8	138	3.8	6.7	2.05	108	384	15.5	0.60	3.7	160	0	10.8
3/9	16.8	142	10.9	5.6	105	7.6	8.1	1.31	151	326	19.8	0.56	5.6	78	23	63
4/5	17.7	178	11.4	3.2	156	6.0	5.6	2.79	103	565	29.4	0.46	2.9	153	12	88
4/11	18.6	122	12.1	4.4	99	8.9	4.3	2.32	105	448	23.7	0.60	3.1	125	37	51
4/16	18.6	159	14.5	3.5	86	10.7	4.5	1.93	121	444	21.5	0.40	3.3	104	23	46
4/19	17.3	112	10.9	5.3	99	9.9	7.2	1.38	114	290	14.9	0.80	6.5	80	27	58
3/29	17.7	182	12.0	3.9	130	9.2	5.8	2.23	147	597	24.0	0.55	4.5	126	33	71
4/11	20.9	152	13.7	2.8	134	5.3	7.5	1.79	84	287	19.4	0.31	2.9	86	19	64
5/12	13.0	101	13.1	5.4	74	12.3	5.7	1.29	120	296	15.9	0.59	4.7	100	29	57
5/14	14.8	98	14.4	9.3	100	15.3	9.0	1.11	118	248	7.8	1.08	9.5	76	25	68
5/20	22.0	108	10.5	4.6	103	12.5	5.6	1.79	110	479	18.2	0.73	6.9	81	29	17
3/14	20.0	177	14.2	9.3	172	9.7	5.9	2.90	127	665	19.5	0.66	4.0	115	33	86
3/20	15.5	115	17.1	6.4	113	10.9	9.2	1.23	106	249	9.9	0.63	5.9	79	22	77
3/15	21.6	180	17.2	7.7	150	15.1	8.9	1.68	79	564	26.4	0.73	7.8	78	15	70
5/26	21.1	144	11.2	3.9	111	8.4	6.3	1.77	150	505	26.4	0.58	4.7	84	35	63
3/12	17.6	134	12.1	6.2	115	13.4	8.2	1.41	80	204	6.5	0.94	8.9	80	15	65
3/26	123	123	12.6	5.8	130	7.9	5.1	2.56	144	701	28.6	0.77	3.7	173	57	88
3/22	13.5	99	9.8	4.7	98	7.9	6.5	1.50	130	372	23.5	0.80	5.3	111	40	74
Average values			13.3	5.3		10.6	7.0		118	378	17.2	0.64	5.7	101	27	
Chest Closed																
1/15	15.0	102	9.4	2.3	82	13	6.8	1.12	75	161	12.4	0.41	4.8	53	9	54
1/11	21.0	172	11.7	2.2	75	8.4	7.7	0.95	61	111	8.6	0.31	6.6	94	12	36
1/16	10.1	95	10.0	4.0	73	8.7	4.7	1.79	74	252	16.6	0.71	4.9	99	20	72
1/22	18.0	123	8.6	3.6	85	8.8	6.1	0.87	80	132	11.0	0.44	5.2	61	11	47
1/17	14.1	102	13.0	3.5	70	3.4	6.7	1.50	109	296	23.6	0.23	2.9	61	17	49
2/7	21.4	178	13.8	2.1	101	6.1	6.8		80	190	14.4	0.46	4.9	74	14	41
Average values			11.0	2.92		7.5										

\* In the last six experiments the chest of the animal was opened and the cannula was inserted through the wall of the chest. This procedure caused, as shown by the average figures, a decline in the cardiac consumption of oxygen, cardiac output, blood pressure, cardiac work and cardiac efficiency.

attributed to the fact that in the present study only large dogs were used and that since the output of the heart is more nearly related to body surface than to body weight (Grollman<sup>11</sup>) large dogs tend to have a lower output per unit of body weight than do smaller animals

Under resting conditions the work of the heart varied between 14 and 7 kilogrammeters per minute, the average being 38. The values are considerably higher than those reported by Evans and Matsuoka,<sup>12</sup> the difference probably being attributable to the larger size of our dogs and to the greater output of the heart of the intact animal as compared with that of the heart-lung preparation. Per gram of heart the cardiac work per minute varied between 14 and 57, with an average of 27 grammmeters.

Wide variations in the cardiac efficiency were noted, the values varying between 5.7 and 29.4 per cent, with an average of 17.2 per cent. The variations cannot be explained by differences in the state of the different animals, as they were all in good condition at the time of the experiments and had not been subjected to a major surgical procedure. In general, the efficiency of the heart was higher in these experiments than in those of Evans and Matsuoka. The difference may possibly be ascribed to the slower pulse rate in our animals, for Evans demonstrated that the energy expended for a given amount of work is greater at a rapid than at a slow pulse rate.

*The Effect of Increase in Work on the Mechanical Efficiency of the Heart*—In a number of experiments study has been made of the effects of increasing the work by infusions, by injecting epinephrine and by clamping the carotid arteries. The data are shown in the first six experiments listed in table 4. In these experiments a striking increase in the coronary blood flow and in the cardiac consumption of oxygen occurred. The proportion of the total oxygen absorbed which was used by the heart increased strikingly in four of the six experiments. Diminution in the systemic arteriovenous oxygen difference and marked increase in the output of the heart occurred in each instance. The mechanical efficiency of the heart likewise underwent a striking increase in each of the experiments. This observation is in accord with those of Evans and Matsuoka, who noted that in the heart-lung preparation an increase in the work of the heart within physiologic limits was associated with augmented efficiency of its activity.

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11 Grollman, A. *The Cardiac Output of Man in Health and Disease*, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 86.

12 Evans, C. L., and Matsuoka, Y. *The Effect of Various Mechanical Conditions on the Gaseous Metabolism and Efficiency of the Mammalian Heart*, J. Physiol. **49** 378, 1915.

That a rise in the cardiac output without an associated elevation of blood pressure may cause an increase in mechanical efficiency and in the coronary blood flow in the intact animal was proved in one experiment (table 4, experiment conducted on June 18) in which the blood pressure remained practically constant

TABLE 4—*The Effect of Increase in Work on the Mechanical Efficiency of the Heart*

Date, 1934	Weight of Animal, kg	Conditions	Coro- nary Flow per Min Cc	Mean Arte- rial Blood Pres- sure, Mm of Hg	Per- cent age of Total Oxy- gen Used by Heart	Ar- tero- venous Oxy- gen Dif- fer- ence, Vol %	Car- diac Out- put per Min Liters	Me- chan- ical Effi- ciency of Heart
1/17	14.0	Control	45	80	8.4	8.09	0.87	11.0
		After infusion of 200 cc of blood + 1 mg of epinephrine, carotid arteries clamped, vagi cut	321	340	35.3	3.73	1.96	24.0
1/22	18.1	Control	87	100	8.8	4.74	1.79	16.6
		After infusion of 500 cc of acacia + 1 mg of epinephrine	770	244	38.0	1.10	10.20	40.0
		After withdrawal of 600 cc of blood	179	81	14.2	5.24	1.26	7.5
1/16	10.0	Control	63	61	8.7	7.66	0.95	8.6
		After infusion of 500 cc of acacia + 1 mg of epinephrine	348	140	17.3	2.00	4.25	37.6
1/11	20.9	Control	54	75	8.4	6.75	1.12	12.4
		After infusion of 500 cc of acacia, carotid arteries clamped	137	124	10.2	3.81	3.23	29.6
6/18	15.9	Control	67	81	10.1	10.15	0.89	7.5
		After infusion of 1.75 liters of saline solution intravenously	133	84	15.0	1.72	6.36	30.3
3/5	19.0	Control	147	138	23.5	8.10	1.20	6.1
		Control	140	132	22.3	7.61	1.28	6.6
		After infusion of 2.7 liters of saline solution intravenously						
		Immediately	460	176	21.2	3.31	4.15	20.6
		Thirty minutes	384	108	24.6	6.50	1.58	5.9
4/4	21.8	Control	63	130	4.9	10.51	1.59	23.1
		Control two hours later	88	114	5.1	8.36	1.82	24.7
		After infusion of 1,100 cc of saline solution into coronary sinus	188	116	7.4	5.07	3.22	28.9
		After infusion of 2,400 cc of saline solution into coronary sinus	235	82	6.9	4.36	3.76	25.1
4/2	10.9	Control	80	101	13.8	7.73	0.91	8.9
		After infusion of 400 cc of saline solution into coronary sinus	331	79	16.6	4.79	1.42	9.2
2/7	24.8	Control	44	109	6.1	6.75	1.50	23.6
		Anoxemia	253	126	16.4	3.14	2.35	21.6
2/12		Control	109	70	9.7	2.44	3.25	29.3
		Anoxemia + 1 mg of epinephrine	650	180	50.4	2.00	1.44	14.4

In a number of experiments attempts were made to increase the work of the heart by measures which might at the same time impair its activity. When saline solution, instead of being infused into the femoral vein, was introduced into the coronary sinus in large amounts (table 4, experiments conducted on April 2 and 4) the coronary flow and the cardiac output increased, but the blood pressure and the mechanical efficiency of the heart failed to rise significantly. It is possible



that the inability of the heart to respond to an increase of work with a rise in its efficiency may be related to temporary edema of the heart muscle as the result of the infusion of saline solution into the coronary sinus

The effects of anoxemia were evident in the last two experiments listed in table 4. Again, in spite of the rise in blood pressure and the marked increase in the coronary blood flow, the efficiency of the heart did not increase but remained constant in one experiment and diminished in the other. The experiments in table 4 appear to indicate that the normal cardiac response to a greater load with augmented efficiency is prevented when the increase in work is accompanied by measures which injure the heart.

TABLE 5—*The Effect of Chloroform on the Mechanical Efficiency of the Heart*

Date, 1934	Weight of Dog, kg	Conditions	Coro- nary Flow per Min Cc	Mean Arte- rial Pres- sure, Mm of Hg	Per- cent age of Total Oxy- gen Used by Heart	Ar- terio- venous Oxy- gen Dif- fer- ence, Vol %	Car- diac Out- put per Min, Liters	Me- chan- ical Effi- ciency of Heart	Comment
3/15	21.6	Control	131	107	15.1	8.95	1.68	5.7	
		After chloroform	123	84	14.3	8.96	1.47	4.5	{Chloro form inhaled
		After chloroform	124	83	17.0	8.95	1.33	3.8	
		After chloroform	113	61	16.3	8.48	0.99	3.0	
3/26	14.8	Control	95	144	9.2	5.03	2.56	28.6	
		Control	92	141	10.0	4.34	2.67	30.1	
		After 0.2 cc chloroform*	83	110	12.1	3.39	2.49	25.3	
		After 0.9 cc chloroform*	52	68	13.2	1.69	1.84	23.2	Moribund
3/20	15.5	Control	72	106	10.9	9.18	1.23	9.9	
		After 1.9 cc chloroform*	60	76	17.5	7.98	0.51	5.0	
3/22		Control	79	130	7.9	6.53	1.50	23.5	
		After 1.7 cc chloroform*	37	46	21.3	12.44	0.12	1.5	Moribund

\* The chloroform was injected intravenously

*The Effect of Chloroform on Cardiac Efficiency*—The summarized data on four experiments are presented in table 5, and the complete data from one experiment are shown in table 6. The initial change in most of the experiments was a decline in the arterial blood pressure. Since this usually preceded a decrease in the cardiac output, it was probably due to a peripheral action of the drug. The later decline in blood pressure was accompanied by, and presumably due to, a diminution in the cardiac output.

Concurrently with the fall in arterial blood pressure the oxygen consumption of the animal declined, and at the same time the proportion of the total intake of oxygen used by the heart increased, although the actual oxygen consumption of the heart did not always rise. The work done by the heart diminished as the blood pressure declined and then decreased still further with the fall in cardiac output. Significant

diminution in the latter function occurred in each experiment. The cardiac output in proportion to the metabolism was unchanged in one experiment, markedly increased in one, slightly increased in one and markedly decreased in two. The mechanical efficiency of the heart was strikingly diminished in four of the five experiments, no significant change being noted in one instance. In the latter experiment, that of March 26, the animal was moribund at the time of the last observation, and it is probable that an oxygen debt was accumulating in the heart. In general, the decline in the cardiac output and the mechanical efficiency tended to occur together.

TABLE 6—Complete Data on One Experiment on the Effect of Chloroform on the Heart \*

Conditions	Control		Inhaling Chloroform		
	Control	Control	101	88	81
Oxygen consumed per minute, cc	172	171	101	88	81
Oxygen content of arterial blood, vol %	19.42	20.50	19.36	18.40	17.30
Oxygen content of mixed venous blood, vol %	13.49	14.76	8.58	7.44	4.84
Systemic arteriovenous oxygen difference, vol %	5.93	5.74	10.78	10.96	12.46
Oxygen content of coronary venous blood, vol %	5.26	3.98	5.08	4.66	3.15
Coronary arteriovenous oxygen difference, vol %	14.16	16.52	14.28	13.74	14.15
Coronary flow per min, cc	117	110	108	60	43
Cardiac consumption of oxygen, per minute, cc	16.6	18.2	15.4	8.25	6.08
Percentage of total oxygen used by the heart	9.7	10.6	15.3	9.6	7.5
Mechanical equivalent of cardiac oxygen, kilogram meters per min	34.0	37.3	31.6	16.9	12.5
Cardiac output per min, liters	2.90	2.98	0.94	0.78	0.65
Mean arterial blood pressure, mm of Hg	127	116	58	43	33
Work of left ventricle, kilogrammeters per min	4.99	4.69	0.72	0.45	0.29
Assumed work† of right ventricle, kilogrammeters per min	1.66	1.57	0.24	0.15	0.10
Total cardiac work, kilogrammeters per min	6.65	6.26	0.96	0.60	0.39
Mechanical efficiency of heart	19.5	16.8	3.0	3.5	3.1

\* The weight of the dog was 19.1 Kg, and the weight of the heart was 117 Gm.

† The work of the right ventricle is assumed to be one third that of the left.

The experiments with chloroform were complicated by the peripheral effect of this drug, which renders difficult the interpretation of results. From the observations it is not possible to say whether the essential physiologic change in the heart was the diminution in output or the decline in efficiency, since the two changes tended to occur together. However, the observations indicate clearly that an increase in the arteriovenous oxygen difference as the result of diminished cardiac output in proportion to metabolism is not an essential feature in heart failure.

*The Effect of Potassium Chloride on Cardiac Efficiency*—Four experiments are summarized in table 7, and the complete data on one experiment are shown in table 8. During the slow intravenous administration of potassium chloride, the mean blood pressure tended to remain fairly constant, occasionally exhibiting a temporary increase, which was followed in several instances by a sharp decline, with recovery if the injections were temporarily discontinued. Constant effects on the coronary blood flow were not noted, but the function was considerably

increased in some stage of all the experiments. The oxygen consumption of the animal underwent no constant changes, but the percentage of the total amount of oxygen used by the heart tended to increase

TABLE 7—*The Effect of Potassium Chloride on the Mechanical Efficiency of the Heart*

Date, 1934	Weight of Dog, Kg	Conditions	Coronary Flow per Min Cc	Mean Arterial Pressure, mm Hg	Percentage of Total Oxygen Used by Heart	Arteriovenous Oxygen Difference, Vol %	Cardiac Output per Min Liters	Mechanical Efficiency of Heart
5/20	22.1	Control	103	140	12.5	5.59	1.79	18.2
		Control	100	138	12.3	5.82	1.72	18.0
		After 1.6 Gm potassium chloride	86	136	15.8	6.30	1.37	12.7
		After 2.8 Gm potassium chloride	148	136	10.1	7.36	2.01	16.9
3/23	17.7	Control	100	147	9.2	5.82	2.23	24.0
		Control	95	147	8.4	6.90	2.22	22.6
		After 0.3 Gm potassium chloride	122	142	11.1	5.57	2.75	20.3
		After 0.6 Gm potassium chloride	110	134	11.2	6.40	2.11	16.5
		After 3.7 Gm potassium chloride	100	117	9.8	10.89	1.34	9.7
5/12	13.0	Control	74	120	12.3	5.75	1.29	15.9
		After 1.25 Gm potassium chloride	88	116	9.3	5.90	1.49	19.6
		After 2.8 Gm potassium chloride	52	45	22.1	12.24	0.43	1.6
4/5	17.6	Control	82	106	6.0	5.60	2.79	29.4
		After 1.9 Gm potassium chloride	57	102	6.6	6.97	1.66	20.5
		After 3.1 Gm potassium chloride	140	102	8.3	5.75	2.42	19.9

TABLE 8—*Complete Data for One Experiment on the Effect of Potassium Chloride on the Heart\**

Conditions	Control	After 3 Gm Potassium Chloride	After 4.8 Gm Potassium Chloride
Oxygen consumed per minute, cc	126	99	121
Oxygen content of arterial blood, vol %	17.43	15.66	15.06
Oxygen content of mixed venous blood, vol %	9.81	8.83	7.99
Systemic arteriovenous oxygen difference, vol %	7.62	6.83	7.07
Oxygen content of coronary venous blood, vol %	6.66	4.00	2.42
Coronary arteriovenous oxygen difference, vol %	10.77	11.66	12.64
Coronary flow per minute, cc	42	42	72
Cardiac oxygen consumption per minute, cc	4.5	4.9	9.1
Percentage of total oxygen used by heart	3.6	5.0	7.5
Mechanical equivalent of cardiac oxygen, kilogrammeters per min	9.3	10.1	18.7
Cardiac output per min liters	1.65	1.45	1.71
Mean arterial blood pressure, mm Hg	64	74	54
Work of left ventricle, kilogrammeters per min	1.51	1.53	1.32
Assumed work† of right ventricle, kilogrammeters per min	0.50	0.51	0.44
Total cardiac work, kilogrammeters per min	2.01	2.04	1.76
Mechanical efficiency of heart	21.6	20.3	9.4

\* The weight of the dog was 20.9 Kg, and that of the heart, 132 Gm

† The work of the right ventricle was assumed to be one third that of the left

Consistent alterations in the cardiac output were not noted, this function remaining relatively constant in some experiments and undergoing temporary changes in either direction in others. In the latter stages of two experiments the cardiac output in proportion to the metabolism was

considerably diminished, but this change was not noted in the other three experiments. The mechanical efficiency of the heart underwent significant decrease in each of the experiments.

The observations indicate that in heart failure produced by potassium chloride the impaired cardiac activity is manifested by a decline in the functional efficiency rather than in the amount of blood expelled. They are in agreement with the results observed in the heart-lung preparation as fatigue of the heart sets in, for here also the essential physiologic change consists in an increased expenditure of energy as dilatation develops rather than a decrease in the performance of work.

#### COMMENT

Since the present study is the last of several devoted to the subject of the pathogenesis of heart failure, it may be permissible to summarize briefly the more important conclusions which have been arrived at in regard to this general problem.

*The Relation of Congestive Heart Failure to the Cardiac Output*—The majority of patients with advanced cardiac disease exhibit a diminution in the minute volume of the heart<sup>1a</sup>. No correlation exists between the degree of decline in this function and the clinical state of the patient. Improvement with disappearance of congestive phenomena may be associated with no change or with alterations in either direction in the cardiac output<sup>13</sup>. In acute experimental heart failure the amount of blood pumped by the heart may or may not be diminished. Experimental procedures, producing hemorrhage and shock, which are regularly associated with marked decline in this function, are not ordinarily accompanied by congestive phenomena.

Diminution in the cardiac output fails to account for the occurrence of edema<sup>14</sup>.

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13 Friedman, Clark, Resnik and Harrison<sup>1b</sup> Friedman, Resnik, Calhoun and Harrison<sup>1c</sup> Resnik, Friedman and Harrison<sup>1d</sup>

14 Edema in patients with heart failure has sometimes been ascribed to an increase in the permeability of the capillaries as the result of diminished circulation through them. Since the capillaries are normally freely permeable to water and to small molecules, such an increase in permeability can account for edema only when it is sufficiently marked to allow the escape of significant amounts of protein into the tissue fluids, with a resultant increase in the colloid osmotic pressure in the intercapillary spaces. However, it has been demonstrated (Gilligan, D. R., Volk, M. C., and Blumgart, H. L. *J. Clin. Investigation* **13** 365 [May] 1934. Schade, H. *Ergebn. d. inn. Med. u. Kinderh.* **32** 425, 1927. Youmans, J. B. Personal communication to the authors) that the edema fluid of persons with congestive heart failure has a low protein content. This observation indicates that increased capillary permeability as the result of diminished circulation is not the essential factor in the production of cardiac edema.

The hypothesis of forward failure (diminished output) fails to account for cardiac dyspnea, for this symptom has been shown to be unrelated to gases in the blood and to either the systemic<sup>1</sup> or the cerebral blood supply<sup>15</sup> in the majority of subjects with congestive heart failure.

Certain patients exhibit simultaneously the clinical phenomena of congestive heart failure and those of circulatory collapse. Such clinical manifestations as a feeble thready pulse, diminution in the blood pressure and the pulse pressure, weakness and, in certain cases, syncope are encountered in persons with coronary thrombosis, acute diphtheritic myocarditis, massive pericardial effusion, chronic obliterative pericarditis and the Stokes-Adams syndrome. In such cases decline in the cardiac output is responsible for the phenomena of circulatory collapse.

As a rule, diminution in the blood supply of the tissue, of sufficient severity to produce symptoms is of peripheral rather than cardiac origin. The clinical picture of shock or collapse (the hypokinetic syndrome) may be brought about by disorders, such as hemorrhage, secondary shock and severe dehydration, which diminish the circulating blood volume (the hematogenic type), by disturbances of the central nervous system, such as fainting, injury to the spinal cord and spinal anesthesia, which lower the blood pressure (neurogenic type), by agents, such as histamine and nitrites, which lower the blood pressure through direct dilation of the vessels (vasogenic type), or by disorders of the heart, such as those mentioned in the previous paragraph, which lead to an excessive and often acute diminution in its output (cardiogenic type). The important point is that a decrease in the amount of blood pumped by the heart, regardless of its underlying cause, is associated not with the congestive but with the collapse type of circulatory failure.

*The Relation of Congestive Heart Failure to Back Pressure*—The idea that the clinical manifestations of heart failure were dependent on back pressure was generally accepted from the time of the publication of James Hope's book until the present century. In more recent years the concept has fallen into disrepute, particularly among British and American clinicians. The chief objection to the back pressure theory has been based on the assumption that it necessarily implies regurgitation through the auriculoventricular valves. This, however, is not true, for the auricular pressure may rise as a result of dilation of the

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15 Cullen, G. E., Harrison, T. R., Calhoun, J. A., Wilkins, W. E., and Tims, M. M. *Studies in Congestive Heart Failure*. XIII. The Relation of Dyspnea of Exertion to the Oxygen Saturation and Acid-Base Condition of the Blood, *J. Clin. Investigation* **10** 807, 1931. Calhoun, J. A., Cullen, G. E., Harrison, T. R., Wilkins, W. E., and Tims, M. M. *Studies in Congestive Heart Failure*. XIV. Orthopnea. Its Relation to Ventilation, Vital Capacity, Oxygen Saturation and Acid-Base Condition of Arterial and Jugular Blood, *ibid* **10** 833, 1931.

ventricle by residual blood, so that a greater pressure gradient is required in diastole in order for the ventricle to receive a given amount of blood. This sequence of events may come about in the absence of regurgitation through either the mitral or the tricuspid orifices. The failure to appreciate properly the fact that back pressure may be the result of changes in pressure during diastole rather than during systole has been responsible for the discredit into which the backward failure theory has fallen.

According to the back pressure theory congestive phenomena may occur either independently or concurrently in the two vascular beds. The work of Eyster<sup>16</sup> and of others<sup>17</sup> has established the fact that when heart failure is associated with engorgement of the liver and subcutaneous edema the systemic venous pressure is elevated. In other patients with heart failure, as revealed by congestive phenomena in the lungs, the systemic venous pressure is normal. Since it is not possible to measure accurately the pressure in the pulmonary veins of man, direct evidence that congestion of the lungs is associated with a rise in the pulmonary venous pressure is lacking. However, convincing, although indirect, evidence along the same line is furnished by measurement of the vital capacity, which is invariably diminished in patients with râles in the lungs or with any considerable degree of cardiac dyspnea.

That failure of one side of the heart only may occur is illustrated by the experiments with chloroform, in which pulmonary edema developed in the animals without a rise of the systemic venous pressure. Such observations cannot be explained on the basis of forward failure and constitute rather conclusive evidence in favor of the hypothesis of backward failure.

The concept of back pressure also furnishes an adequate explanation of the important clinical manifestations of heart failure. Edema is accounted for by the rise in systemic venous pressure. The consequent congestion of the liver suffices to explain its enlargement. Distention of the venules and the venous ends of the capillaries of the skin as a result of the heightened venous pressure accounts for cyanosis. Dyspnea, the most important subjective phenomenon of persons with cardiac failure, has been shown to be dependent in the main on two factors: decrease in respiratory reserve (i. e., in vital capacity), and reflex

16 Eyster, J. A. E. *The Clinical Aspects of Venous Pressure*, New York, The Macmillan Company, 1929.

17 Blumgart, H. L., and Weiss, S. *Clinical Studies on the Velocity of Blood Flow. XI. Pulmonary Circulation Time, the Minute Volume Blood Flow Through the Lungs and the Quantity of Blood in the Lungs*, *J. Clin. Investigation* **6**: 103, 1928. Schott, E. *Die Erhöhung des Druckes im venösen Blute bei Anstrengung als Mass für die Funktionstüchtigkeit des menschlichen Herzens*, *Deutsches Arch. f. klin. Med.* **108**: 537, 1912.

stimulation of respiration<sup>18</sup> Both these results are brought about by engorgement of the lungs as the result of back pressure from a dilated left ventricle or from a contracted mitral orifice Direct proof that an increased amount of blood exists in the lungs of patients with cardiac dyspnea has been afforded by the observations following the application of the injection methods which have been cited<sup>19</sup>

*The Relation of Cardiac Enlargement to Back Pressure and to Congestive Heart Failure*—If one leaves out of consideration certain cases of pericardial disease in which the filling of the heart is impaired by fibrosis or by fluid, it is safe to assert that the one constant postmortem observation in persons dying of congestive heart failure is enlargement of the heart Dilatation of one or both of the ventricular cavities is invariably present, whether the cardiac disorder has been acute or chronic, and in persons with chronic congestive failure hypertrophy of some degree is regularly encountered The failure to appreciate the importance of these observations in the interpretation of the mechanism of congestive failure has led to much unnecessary confusion Studies of the heart-lung preparation have shown that slight degrees of dilatation of the heart, when due to greater work, are associated with increasing mechanical efficiency but that when the dilatation is the result of impairment of the muscle it is accompanied by progressive decline in the efficiency The observations reported in the present paper indicate that these conclusions hold true for the whole animal and suggest that the conclusions arrived at from the study of the heart-lung preparation are applicable to heart failure in the intact organism

The capacity of the heart to increase its work depends on its ability to dilate and thereby expend more energy The heart which is already dilated is drawing on its reserve power and hence has a smaller margin of safety Even so, the failing heart may retain a considerable although much diminished ability to increase its work Under resting conditions congestive heart failure (the dyskinetic syndrome) is characterized not so much by the diminished performance of work as by the necessity to expend more energy in order to perform a given task

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18 Harrison, T R , Harrison, W G , Jr , Calhoun, J A , and March, J P Congestive Heart Failure XVII The Mechanism of Dyspnea on Exertion, *Arch Int Med* **50** 690 (Nov) 1932 Harrison, W G , Jr , Calhoun, J A , March, J P , and Harrison, T R Congestive Heart Failure XIX Reflex Stimulation of Respiration as the Cause of Evening Dyspnea, *ibid* **53** 724 (May) 1934 Harrison, T R , King, C E , Calhoun, J A , and Harrison, W G , Jr Congestive Heart Failure XX Cheyne-Stokes Respiration as the Cause of Paroxysmal Dyspnea at the Onset of Sleep, *ibid* **53** 891 (June) 1934 Harrison, T R , Calhoun, J A , and Harrison, W G , Jr Congestive Heart Failure XXI Observations Concerning the Mechanism of Cardiac Asthma, *ibid* **53** 911 (June) 1934

19 Weiss and Robb<sup>3</sup> Hamilton, Moore, Kinsman and Spurling<sup>4</sup>

It is probable that dilatation in some degree precedes and possibly causes hypertrophy. The latter phenomenon sometimes develops in subjects who have no valvular lesion, no increase in blood pressure and no obvious cause for a general increase in the work of the heart. In such cases areas of disease are usually encountered in the heart muscle. Probably it makes no difference as regards the individual healthy muscle fiber whether it encounters an increased load because of excessive strain on the heart as a whole or because the diseased fibers are unable to carry on their share of the work. In either instance the fiber exposed to overwork tends to become thicker.

Hypertrophy offers a mechanical advantage because the thicker fiber is more powerful. Unfortunately, it carries with it a potential chemical disadvantage which becomes actual once a certain degree of hypertrophy has been exceeded. Normally, animals with thick cardiac fibers have a slow heart rate, and vice versa<sup>20</sup>. The lengthened period of diastole allows more time for the diffusion of oxygen to take place into the thicker fibers and hence for recovery between contractions. As the human heart hypertrophies, its rate does not undergo a corresponding diminution but often increases. The resulting inadequate supply of oxygen to the fibers tends to induce dilatation, which probably again tends to lead to further hypertrophy, and so the vicious cycle proceeds, the energy necessary to accomplish a given work constantly increasing. Eventually the dilatation proceeds to a point where the amount of residual blood in the ventricle begins to offer resistance to the inflow of blood from the auricle. The pressure in the latter chamber rises, the corresponding veins become distended and engorgement ensues in the capillary bed. Since in the majority of patients the underlying disease process is of such a nature as to affect primarily the left side of the heart, congestion of the lungs and dyspnea usually precede systemic engorgement and edema. After a time the increase in pulmonary pressure leads to failure of the right side of the heart by means of a similar chain of events.

This process of backward failure was clearly described by James Hope a hundred years ago. He attributed it to dilatation of the heart. Starling and his co-workers demonstrated that dilatation, when brought about by processes which impair the heart, is associated with inefficient activity. The recent work on the cardiac output of man and the present studies on experimental heart failure in dogs add further confirmation to the conclusions of Hope and of Starling. Congestive heart failure is a matter of inefficiency rather than insufficiency of the myocardium.

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20 Harrison, T. R., Ashman, R., and Larson, R. M. Congestive Heart Failure. XII. The Relation Between the Thickness of the Cardiac Muscle Fiber and the Optimum Rate of the Heart, *Arch. Int. Med.* **49**: 151 (Jan.) 1932. Harrison, T. R. Enlargement of the Heart, *Internat. Clin.* **1**: 39, 1934.



## SUMMARY

A method has been described for measuring the coronary blood flow of the dog by means of a cannula passed through the right external jugular vein into the coronary sinus. With this procedure it is possible to calculate the consumption of oxygen and the mechanical efficiency of the heart under various conditions. The sources of error involved have been discussed.

Values are reported for the coronary blood flow and for the work, oxygen consumption and mechanical efficiency of the hearts of morphinized dogs subjected to no surgical procedure other than the insertion of arterial and venous cannulas. The amount of oxygen consumed by the heart was in general about 10 per cent of that used by the body as a whole. The average value for the mechanical efficiency of the heart was 17 per cent.

An increase in work produced either by increasing the cardiac output or by raising the blood pressure caused an increase in the mechanical efficiency of the heart.

Heart failure produced by chloroform was associated with a decline in arterial blood pressure, in oxygen consumption and in cardiac output. The proportion of the oxygen absorbed by the heart increased, and the mechanical efficiency of the heart diminished. The systemic venous pressure rose only when the animal was moribund. The cardiac output in proportion to the metabolism underwent no constant changes. At autopsy the heart was observed to be dilated and the lungs were edematous.

Heart failure produced by potassium chloride was associated with a rise in systemic venous pressure, but edema of the lungs did not develop. Constant alterations in the arterial blood pressure, cardiac output and arteriovenous oxygen difference were not noted. The cardiac consumption of oxygen increased, and the mechanical efficiency of the heart diminished. Dilatation of the heart was a constant postmortem observation.

The observations support the validity of the backward failure (back pressure) theory of the mechanism of heart failure. They are not in accord with the forward failure (diminished output) hypothesis. They demonstrate that in the intact animal, as in the heart-lung preparation, heart failure is characterized by an increase in the volume of the heart and a decrease in the mechanical efficiency.

# OPTIMUM TIME TO ADMINISTER INSULIN

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There is a controversy as to the optimum time to administer insulin. Many physicians are of the opinion that it should be given immediately before meals, others, within from fifteen to twenty minutes before meals, and still others, a half-hour before meals. The practice of injecting insulin before meals, irrespective of the type of diet, had been universal since the discovery of the hormone.

When the use of insulin in the treatment of diabetes had its inception physicians prescribed diets high in fat and low in carbohydrate, but recently most doctors have adopted diets high in carbohydrate and low in fat. With this change in the proportions of carbohydrate and fat, there comes about a change in the rapidity and amount of absorption of carbohydrate, a change which should influence the time interval for the injection of insulin. I have seen patients with diabetes acquire symptoms of hypoglycemia within five minutes after the injection of insulin and while eating or within thirty minutes or more after eating. It is evident that the interval between the injection of insulin and the eating of food should be the maximum which does not lead to the development of symptoms of hypoglycemia before the carbohydrate of the meal can be absorbed. This interval for injection of insulin should be within from fifteen to twenty minutes after meals, not before.

From observations I have found that in patients not having diabetes the blood sugar is maintained at relatively constant levels except during the period following meals when the dextrose in the food is being absorbed. Then the level of the blood sugar is slightly elevated but within the normal physiologic limits, and frequently toward the end of the absorption, the blood sugar may be reduced below the level during fasting. The reason for this maintenance of the blood sugar at the normal level is that there is, in all probability, a constant production of insulin—a greater production, perhaps, at the peak of absorption of carbohydrate, which further stimulates the islands of Langerhans, causing oxidation of still more dextrose. It appears, therefore, that the control of the secretion of insulin by the islands of Langerhans to insure proper oxidation of carbohydrate is dependent to a large extent on the rate and

amount of absorption of the dextrose of the food Zunz and La Barre<sup>1</sup> found that increase in the pancreatic juice caused by the introduction of hydrochloric acid into the duodenum increased the pancreatic secretion of insulin, as was evidenced by the reduction of the blood sugar content It has been shown definitely in dextrose tolerance tests given to normal persons that repeated doses of dextrose cause hypoglycemia or little or no change in the level of the blood sugar The interesting fact is that in a patient having no diabetes the sugar in the blood frequently falls below the fasting level within two hours after the taking of dextrose, when there is still considerable absorption from the intestine Frank<sup>2</sup> advanced the theory that hypoglycemia of this type is due to overstimulation of the glycogen-forming function of the liver Foster<sup>3</sup> claimed that the first dose of dextrose stimulates the glycogenic mechanism to such activity that the organism is able to deal with any amount of dextrose without becoming hyperglycemic

As to the rate of absorption of carbohydrate or dextrose in normal persons, it has been shown to reach its peak, within the normal range for blood sugar, about thirty minutes after ingestion, as is evinced by specimens of blood taken at thirty minute intervals, samples taken at thirty minute intervals are more informative than those taken at sixty minute intervals<sup>4</sup> After this peak has been reached, the curve descends, not infrequently below the fasting level

Patients with diabetes, on the other hand, react to the absorption of dextrose or carbohydrate with distinct hyperglycemia, because the insulin-glycogen mechanism fails<sup>5</sup> MacLean and de Wesselow<sup>6</sup> presented a comparison of the curves for the blood sugar of a normal man and a patient with diabetes after each had taken 50 Gm of dextrose The curves rise sharply by nearly the same amount for the first hour At this point the curve for the normal subject breaks and soon begins to fall rapidly to the fasting level, whereas the curve for the patient with diabetes continues to rise unchecked for two or more hours, as long as absorption continues Evidently the peak of absorption of dextrose from the meal in the normal person is not the peak in the patient

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1 Zunz, E, and La Barre, J Does the Exocrine Activity of the Pancreas Influence the Secretion of Insulin? *Compt rend Soc de biol* **104** 790, 1930

2 Frank, E Weitere Beitrage zur Physiologie des Blutzuckers, *Ztschr f physiol Chem* **70** 291, 1910-1911

3 Foster, G L Studies on Carbohydrate Metabolism, *J Biol Chem* **55** 303, 1923

4 Exton, W G, and Rose, A R Diabetes as a Life Insurance Selection Problem, *Proc A Life Insur M Dir America* (1931) **18**:252, 1932

5 Exton, W G, and Rose, A R The One-Hour Two-Dose Dextrose Tolerance Test, *Am J Clin Path* **4** 381 (Sept) 1934

6 MacLean, H, and de Wesselow, O L V The Estimation of Sugar Tolerance *Quart J Med* **14** 103, 1921

with diabetes This is so because the production of insulin in the latter is defective and not sufficient to oxidize the carbohydrate, with the result that much escapes combustion and accumulates The extent of the hyperglycemia is, in all probability, dependent on the degree of damage to the insulin-secreting mechanism, the islands of Langerhans, which affect rate and amount of absorption of carbohydrate Allen<sup>7</sup> gave his paradoxical law based on animal experiments as follows "Limits of tolerance in non-diabetic animals are all apparent, not real There is no real limit of the power of utilizing sugar except death The paradoxical law of dextrose distinguishes sharply between diabetic and every type of non-diabetic animal Limits of tolerance in diabetic animals are real and not apparent Just the opposite of the paradoxical law"

Since the present-day dietary treatment for diabetes is to give a diet higher in carbohydrate, as advocated by Gray and Sansum,<sup>8</sup> Thomas and Howard,<sup>9</sup> Richardson<sup>10</sup> and others, rather than diet lower in carbohydrate and higher in fat, as advocated by Newburgh and Marsh<sup>11</sup> the absorption of dextrose from the meal takes place more rapidly This is, of course, subject to considerable variation in different persons In addition, the absorption, besides being sudden, is prolonged, perhaps, by the proteins and fats, which respond to the insulin more slowly Various gastric or intestinal disturbances may also prolong and interfere with the absorption Absorption under such conditions may prolong the hyperglycemia by four or more hours, before the blood sugar returns to its original fasting level Rehfuess<sup>12</sup> found that the stomach took, on an average, four hours and two minutes to digest a meal consisting of 100 Gm of potatoes, 40 Gm of butter and 100 Gm of hamburger steak In dextrose tolerance tests in which only dextrose and water are given to the patients with diabetes and there is no interference by other foods absorption is almost immediate, so that following ingestion three or more hours elapse before the blood sugar returns to the fasting level, as is evidenced by the hyperglycemia revealed in the blood sugar tests at thirty minute intervals

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7 Allen, F M Glycosuria and Diabetes, Boston, W M Leonard, 1913, p 1179

8 Gray P A, and Sansum, W D The Higher Carbohydrate Diet Method in Diabetes Mellitus, J A M A **100** 1580 (May 20) 1933

9 Thomas, H M, Jr, and Howard, J E Higher Carbohydrate Diet in Diabetes Mellitus, Virginia M Monthly **59** 516 (Dec) 1932

10 Richardson, Russell High Carbohydrate Diets in Diabetes Mellitus, Am J M Sc **177** 426 (March) 1929

11 Newburgh, L H, and Marsh, C Further Observations on the Use of a High Fat Diet in the Treatment of Diabetes Mellitus, Arch Int Med **31** 455 (April) 1923

12 Rehfuess, M E Proteins Versus the Carbohydrates An Inquiry into Their Gastric Digestion, J A M A **103** 1600 (Nov 24) 1934

Physiologic data indicate that the maximum effect of insulin may be secured from one half to three quarters of an hour after injection<sup>13</sup> This, of course, is also subject to individual variation I have found reactions to insulin within five minutes after injection It is evident from clinical observations that the rate of absorption of insulin depends further on the condition of the cardiovascular system, on the patient's age and on the duration of the diabetes In adults who have diabetes of such long duration that advanced premature arteriosclerosis has taken place the circulation is not so responsive as it is in normal persons, and there is a decrease in the volume per minute<sup>14</sup> This decrease may cause a delay in the absorption of insulin, for in young adults with diabetes of short duration, in whom arteriosclerosis is not so extensive or has not made its appearance, there is more rapid absorption of insulin Fletcher and Campbell<sup>15</sup> tabulated results obtained in five normal persons and fifteen patients with diabetes when insulin was given in the morning before breakfast after a sample of blood was taken for the determination of the sugar content Further samples were taken at intervals of one hour for four hours It was noted that the extent of the fall in the blood sugar did not bear any accurate relationship to the amount of insulin given, in one patient 20 units brought about a greater fall than 30 units did, a fall almost as great as that which 50 units caused Macleod<sup>16</sup> described an experiment in which a group of animals was starved for twenty-four hours before insulin was given intravenously and in varying doses The level of the blood sugar came down very rapidly and was lowest in about half an hour after the injection had been made This was interesting because of the fact that within very wide limits of dosage the level of the blood sugar came down in different animals at exactly the same rate

Realizing that there is a rapid and prolonged absorption of carbohydrate from a meal in a patient with diabetes I decided to determine how soon hyperglycemia took place after a meal higher in carbohydrate so as to estimate the optimum time for administering insulin to secure its more complete utilization in oxidizing the dextrose from the food first instead of that present after fasting

Clinical data have shown that if insulin is given at an interval which causes rapid oxidation of the dextrose present after fasting to the extent

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13 Best, C H Personal communication to the author on Nov 17, 1934

14 Ernestene, A C, and Altschule, M D The Effect of Insulin Hypoglycemia on the Circulation, *J Clin Investigation* **10** 521, 1931

15 Fletcher, A A, and Campbell, W R Blood Sugar Following Insulin Administration and Symptoms Complex Hypoglycemia, *J Metabolic Research* **2** 637 (Nov-Dec) 1922

16 Macleod, J J R, and Banting, F G The Antidiabetic Functions of the Pancreas and the Successful Isolation of the Antidiabetic Hormone—Insulin The Beaumont Foundation Lectures, St Louis, C V Mosby Company, 1923, p 46

of producing hypoglycemia before the carbohydrate of the meal can be absorbed, the patient is exposed to serious deleterious effects. This is more apparent in an elderly diabetic patient with advanced cardiovascular disease, in whom the effect may vary from the precipitation of an attack of angina<sup>17</sup> to actual fatality<sup>18</sup>. Turner<sup>19</sup> cited the occurrence of attacks of angina dependent on insulin shocks. Wohlwill<sup>20</sup> found marked changes in the brain cells caused by an overdose of insulin. Blotner<sup>21</sup> cited reports of death from cardiac infarction due to too sudden reduction of the blood sugar following injection of insulin. Ravid<sup>22</sup> reported a case in which when insulin therapy was given marked progression of a retinal involvement developed, evinced by numerous small hemorrhages in both fundi. "As long as we find such severe complications with the overdose of insulin, we must strongly advise against the method of forcing the administration of insulin until mild reactions are encountered."<sup>23</sup>

If patients took their insulin after their meals, would not the reactions or shocks that occur be less severe and harmful? They would be less severe because there is available the dextrose of the food, plus, perhaps, that present after fasting to offset the tendency toward a decreased reserve of glycogen. If the insulin is given before the meal there is only the dextrose present after fasting with no carbohydrate of the food available, thus encouraging a tendency toward decreasing the glycogen reserves throughout the body through the necessity to reconvert glycogen to dextrose to compensate for the deficiency in blood sugar.

From past clinical and experimental observations there were reasons enough to believe that if insulin were given at the inception of the increase in hyperglycemia induced by the absorption of the carbohydrate of the food, detrimental effects would be less marked. Thus I proceeded to determine the rapidity of onset of the hyperglycemia produced by the regular diet prescribed for a group of patients with diabetes.

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17 Parsonet, A. E., and Hyman, A. S. Insulin Angina, *Ann Int Med* **4** 1247, 1931.

18 Gigon, A. Diabetes and Insulin Therapie, *Schweiz med Wchnschr* **53** 882, 1923, *Klin Wchnschr* **2** 1670, 1923.

19 Turner, K. B. Insulin Shock as the Cause of Cardiac Pain, *Am Heart J* **5** 671, 1930.

20 Wohlwill, F. Ueber Hirnbefunde bei Insulin-Ueberdosierung, *Klin Wchnschr* **7** 344, 1928.

21 Blotner, H. Coronary Disease in Diabetes Mellitus, *New England J Med* **203** 709, 1930.

22 Ravid, J. M. Transient Insulin Hypoglycemia Hemiplegia, *Am J M Sc* **175** 756, 1928.

23 Rudy, A. Hazards in the Treatment of the Elderly Diabetic with a Report of Cases, *Endocrinology* **17** 309 (May-June) 1933.

who had been treated previously with a diet or with both insulin and a diet. The patients, selected from the clinic for patients with diabetes at the Lankenau Hospital, were of various ages and had from mild to extensive sclerosis of the cardiovascular system, a factor which perhaps affects the rate of absorption of the carbohydrate of the food. The diets were higher in carbohydrate. Carbohydrate averaged from 100 to 180 Gm, fat from 80 to 100 Gm and protein from 50 to 80 Gm. Sister Maude Dehrman, the chief dietitian, with the aid of

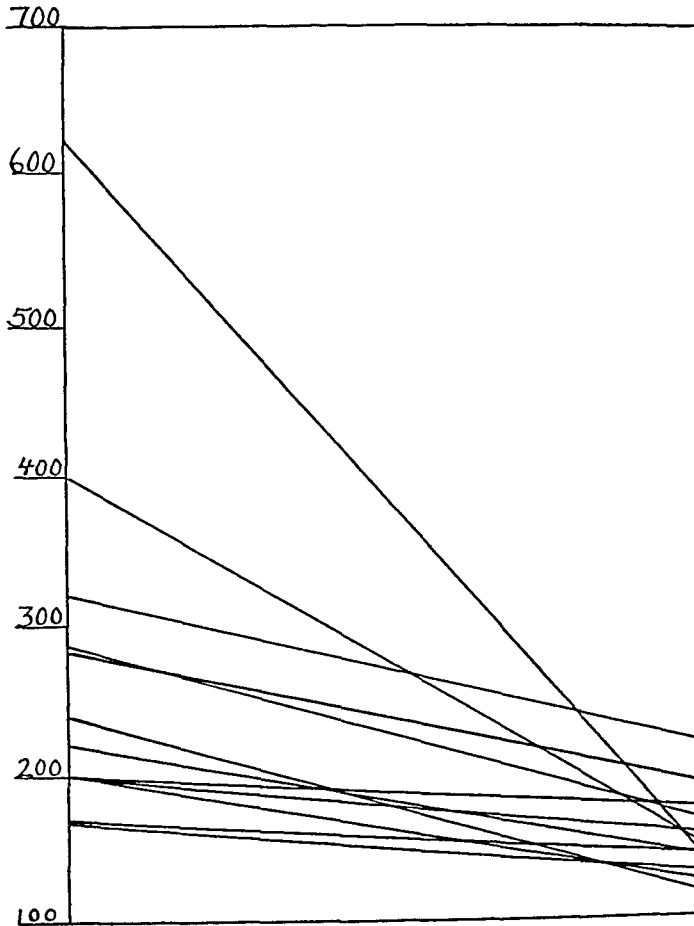


Chart showing the reduction in blood sugar in patients taking insulin after meals for an average of forty days. The figures at the left indicate the initial level.

Miss Ethel Hobson, prepared and weighed the food. Miss Beñta Schubert made the examinations for blood sugar (Folin-Wu). Each patient was given his regular weighed breakfast. An estimation of the blood sugar was made before the meal, immediately after the meal and again in from fifteen to twenty minutes—three examinations of the blood. Table 1 lists the group examined showing the age and weight of each patient, the duration of the diabetes, the previous treatment

with diet or with both insulin and diet, the complications present, if any, and the values for the blood sugar determined after fasting, immediately after the meal and again in from fifteen to twenty minutes

TABLE 1—Data on Patients with Diabetes Taking Insulin After Meals

Patient	Age	Weight, Lbs	Duration of Diabetes, Years	Previous Treatment Diet or Both Insulin and Diet	Complications Present	Blood Sugar Values		
						After Fasting	Imme- diately After Eating	From 15 to 20 Minutes After Eating
A A	49	228	1	Diet	None	200	210	220
E K	72	153	28	Both	None	320	340	450
W B	15	139	2	Both	None	100	330	340
J K	57	165	10	Both	None	220	255	215
J S	48	140	5	Diet	None	160	140	190
L R	24	166	1	Both	None	110	115	165
T C	50	139	6	Diet	None	95	150	145
A P	63	124	20	Both	None	145	225	250
E J	51	150	5	Both	None	225	270	380
L B	62	146	4	Diet	None	100	120	150
N B	47	139	5	Both	None	280	270	260
S R	23	118	2	Diet	None	100	125	115
H G	14	113½	4	Both	None	270	390	400
D M	18	128	3	Both	None	260	255	325
G B	28	115	4	Diet	None	120	145	125
J W	55	129	9	Both	None	320	268	337
A P	50	131	6	Diet	None	120	140	165
M M	60	130	18	Diet	Gangrene of right foot	140	150	115
C K	65	165	18	Both	Neuritis of right lower extremity	130	250	225
B H	40	131	7	Both	Carbuncle on neck	150	130	140

## SUMMARY

The administration of insulin after meals has proved to be advantageous to the patient in several ways, and for comparison I have tabulated the observations with both methods thus

Point of Comparison	Insulin Before Meals	Insulin After Meals
Occurrence of hypoglycemia caused by insulin	More liable	Less liable
Storage of glycogen	Good	Better
Utilization of insulin	More complete oxidation of sugar present after fasting, less of sugar from the meal	More complete oxidation of sugar from the meal, perhaps more gradual oxidation of that present after fasting as evidenced by reduction in fasting blood sugar
Deleterious effects	More liable	Less liable
Effect of taking insulin in advance cardiovascular sclerosis with impairment of heart	Dangerous	Safer
Response	Good	Better
Disposition of patient	Frequently disturbed	Less disturbed
Influence of diet higher in carbohydrates	Good	Better
Attitude of hospital patients toward injection	Good	Better
Effect on diabetes mellitus	Good	Better, more rapid improvement evidenced by reduction in blood sugar and in total dose of insulin and by general physical condition of patient
Patient	Contented	More contented



TABLE 2—Data on the Results Obtained in a Group of Patients Taking Insulin After Meals

Patient	Age, Years	Weight, Lbs		Blood Sugar at End of Fasting, Mg per 100 Cc		Duration of Diabetes	Total Reduc- tion in Insulin, Units	Complications Present	Comment
		Past	Present	Initial Level	Present Level				
G M	65	161½	163	200	122	2 months	10	Cataracts in both eyes	No insulin reactions, method most practical
E B	58	159	159	166	141	3 months	10	None	Feels well, enjoys meals better than when treated by other method
M R	40	109	178	165	140	3 months	15	None	Does not hurry in eating food, finds method most practical
J S	56	140	140	160	130	2 months	5	Cataracts in both eyes	More convenient to take insulin after meals
N B	65	150	152	230	140	6 weeks	5	None	No insulin reactions, feels well
J W	55	126½	127	320	220	8 weeks	15	Patient appears to be "insulin resis- tant", while fasting has had an average of 380 mg of sugar per 100 cc of blood	Prefers taking insulin after meals
L M	47	150	127½	286	165	10 days	20	Acute dysentery, nausea and vomit- ing	Blood sugar easily controlled
B H	16	130	130	200	175	2 weeks	5	Coryza	Has had no "shocks," which is some what unusual for this patient
H G	11	100	100	400	150	3 weeks	10	None	Blood sugar has never been reduced so low without "insulin shock."
O B	63	128	130	620	140	1 weeks	0	Cataracts in both eyes, gangrene in both legs, patient is about to have bilateral amputation	Patient has had no "insulin shocks" taking insulin after meals has proved to be most practical, because loss of appetite caused irregularity of meal time
A C	63	150½	150	200	166	4 weeks	5	None	Likes this method better than others
E R	60	151	150	193	160	6 weeks	8	None	Method more practical and more convenient
A K	58	165½	167	275	190	3 weeks	15	None	Feels well, idea of injection after meals "good"
A S	59	164½	163	200	180	4 weeks	None	None	Method most practical for her, likes idea
H M	65	108	202	254	129	3 weeks	20	None	"No shock" feels "fine" difficult to reduce sugar on other method

Therefore, I strongly advocate that when insulin is indicated for patients on diets high in carbohydrate it be given within from fifteen to twenty minutes after the meal

Thus there were patients with diabetes who immediately after breakfast showed the blood sugar slightly decreased from the fasting level. Perhaps the little dextrose that was absorbed in a short interval after the meal stimulated the islands of Langerhans, the insulin-secreting mechanism, to the extent that sufficient insulin was secreted to oxidize the carbohydrate, but as the absorption continued, the islands, damaged perhaps by infection or inflammation, or with their function inhibited by neurogenic or endocrine disturbances, were unable to secrete sufficient insulin to oxidize the increasing dextrose from the meal with the result that much escaped combustion had accumulated, producing an increase in the hyperglycemia.

The patients who showed a sudden rise in blood sugar immediately after eating demonstrated perhaps that the insulin-secreting mechanism was extensively damaged. There was insufficient insulin to oxidize the rapidly absorbed carbohydrate of the meal, with the result that a large percentage of the dextrose escaped oxidation and accumulated. This type of rapidly increased hyperglycemia is usually extended several hours before the blood sugar returns to the original fasting level, in the meantime, it causes extensive metabolic disturbances.

It is evident from these observations that if insulin were given within fifteen or twenty minutes after the meal, at the inception of the increase in hyperglycemia following ingestion of food, there would be more complete utilization of the insulin. The results would be (1) better and more complete oxidation of the carbohydrate of the meal, (2) better storage of glycogen, (3) less likelihood of producing hypoglycemia, (4) an increased margin of safety against the deleterious effects of insulin "shock" on the already damaged cardiovascular system of the elderly patient with diabetes, and (5) generally better response to insulin therapy. Such effects have been evident in patients taking insulin after meals, and these patients have always professed the greatest satisfaction. The anxiety caused by having to eat a meal within fifteen minutes after an injection of insulin often caused a patient much mental disturbance and frequently precipitated "mild shock." Often, if a patient received a meal at the end of the usually required interval after an injection of insulin, he hurried in eating the food in order to offset any possibility of insulin "shock," and not infrequently such a reaction occurred. Often a patient disliked the idea of having to take insulin before meals, and this frequently disturbed the disposition. On the other hand, a patient often had a reaction to insulin when there was an undue delay in serving the tray. Then there were times when the tray

arrived before insulin was given, and the patient had to wait, a delay which often caused the food to become cold and unappetizing

When insulin is given after meals, all these disadvantages are eliminated. Already patients have shown improvement by a reduction in the blood sugar and in the total dose of insulin and by an improvement in the general well-being. Table 2 lists a few of the many patients taking insulin after meals, with the effects and comments.

# CLASSIFICATION OF CHRONIC GASTRITIS WITH SPECIAL REFERENCE TO THE GASTRO- SCOPIC METHOD

STUDY BASED ON 1,200 CASES

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Our purpose in this paper is to present our classification of chronic gastritis on the basis of the gastroscopic picture and the prognosis

The term chronic gastritis is applied to nonspecific inflammatory changes in the gastric mucosa or to their end-results. The question at once arises as to whether these changes can be subdivided into types. We believe, on the basis of our experience, that chronic gastritis can be subdivided into four types, which differ in the gastroscopic picture and the prognosis.

## HISTORICAL INTRODUCTION

The existence of chronic gastritis was denied for several decades. Only a few investigators consistently defended its occurrence, notably, Faber and Kuttner. Even today it is often necessary to offer proofs of its existence. This seems strange, for in the mucous membranes of other regions of the body inflammation is the most common disease. The question then at once arises: How can such an extensive mucous membrane as that of the stomach remain free from inflammatory changes? The possibility of a specific protection against inflammation might be raised, but, to our knowledge, it has not been suggested. The opinion that chronic gastritis does not exist evidently arose from the fact that it is difficult to demonstrate chronic gastritis anatomically, either grossly or histologically. The stomach of the cadaver always shows marked pathologic changes, most of which, however, were early recognized as postmortem changes. There was no way to prove a diagnosis of gastritis during life. Therefore the conception of this disease entirely disappeared. The occurrence of acute gastritis, on the contrary, has always been admitted, but the diagnosis was made on clinical grounds only and without morphologic confirmation.

Within the past two decades the great frequency of chronic gastritis has again been recognized. Two methods of research have been responsible for this swing in the opposite direction, namely, microscopic examination of the freshly resected specimen (especially by Faber, Stoerk and Konjetzny) and systematic gastroscopic examination (by one of us [R S] and contemporaries). Attempts at diagnosis by the roentgen relief method have followed—a poor third. No clear clinical picture has yet been established.

#### HISTOLOGIC METHOD AND CLASSIFICATION

The normal histologic appearance of the mucous membrane of the human stomach is not well known. The problem is difficult to approach. Postmortem changes due to autolysis arise so quickly that it is practically impossible to inject a fixative solution sufficiently rapidly into the stomach to allow study of the structure of the mucous membrane as it is during life. The freshly resected specimen can be fixed immediately, but for two reasons the examination of these specimens is also rendered somewhat useless for the purpose. First, resection of the stomach is not carried out in healthy persons but only in patients who are suffering from some disease of the stomach, and, second, it is difficult to decide whether or not resection itself causes histologic changes during the time in which the circulation of the blood is interrupted by ligatures.

Nevertheless, the most marked changes have formerly been clearly observed. They were described as representing three forms of gastritis: gastrite parenchymateuse, gastrite interstitielle and gastrite mixte (Hayem), or as two main forms: hypertrophic gastritis and atrophic gastritis (Kaufmann). Lubarsch expressed the belief that chronic gastritis has a progressive atrophic character, interrupted by hyperplastic formations.

In the decades in which the entity was neglected because of the dominance of functional methods of diagnosis and the impossibility of obtaining a normal picture, these conceptions were forgotten.

New histologic efforts were made by Stoerk, Paschkis, Orator and, especially, Konjetzny. But it must be admitted frankly that the numerous excellent papers and beautiful books published by these authors again lacked the fundamental principle, namely, exact knowledge of the normal mucous membrane. Certain changes in the epithelial cells and cellular infiltration of the interstitium were regarded as pathologic. However, it was not proved whether or not these changes are present in the normal stomach. The curious result was that Paschkis and Orator believed that they noted chronic gastritis in 100 per cent of all adults, while Konjetzny observed chronic gastritis in 100 per cent of all cases of ulcer. It was evident that at least the first of these state-

ments could never be reconciled with the clinical conception of disease. This objection was made early by several German authors, first by Katsch and later by Kalk.

We prefer to consider that the mucous membrane of the adult who has no symptoms is normal, even if histologically the mucous membrane in this case differs from that of the new-born in showing cellular infiltration of the interstitium or minor microscopic differences in the epithelial cells. Such minor changes in the appendix of the adult are no longer classified as appendicitis.

This seems to be the point of view of Beiger, who, in a paper concerning the parietal cells of the stomach, stated that the stomach which shows no gross changes is normal, even though lymphocytic infiltration of the interstitium is noted. His material, however, was much too limited to permit the establishment of an authentic normal histologic picture of the human stomach. Thus, a histologic classification of chronic gastritis is not yet possible. We believe that it will become so later and that our classification on the basis of the gastroscopic examination will be fundamentally in harmony with the histologic classification.

#### GASTROSCOPIC METHOD OF EXAMINATION

The direct examination of the mucous membrane is a reliable universal method of diagnosis when disease is suspected in other body cavities, and since the introduction of the flexible Wolf-Schindler gastroscope, the gastric mucous membrane of every patient, even of the very sick, can be visualized, except in a very few cases in which there is contraindication. Even the deeper-lying lesions can be observed because the superficial layers of the mucosa are transparent.

Because the gastroscopic method depends on the recognition of morphologic changes, it is obvious that one must have an exact knowledge of the normal gastric mucosa as it appears gastroscopically. Early in the course of his gastroscopic investigations, one of us (R. S.) made repeated gastroscopic examinations of the stomachs of healthy adults. The mucous membrane of healthy adults must be considered normal. The danger is in regarding normal variations as pathologic, or vice versa, since gastroscopy is a subjective method of rather recent development. The changes to be described later, however, were not found in the healthy stomach, and for that reason they may legitimately be labeled as disease. They entitle the gastroscopist to conclude that gastritis is better diagnosed at present by means of the gastroscopic method than by the histologic or other methods. We found such changes in about 50 per cent of all the cases in which gastroscopic examination was made.

Before we proceed to a description of the morphologic characteristics of chronic gastritis, one other question should be discussed. Granted that the experienced gastroscopist correctly observes pathologic changes in the mucous membrane, other than the lesions occurring in the well known diseases, such as tumor, ulcer, granuloma, etc., shall he diagnose them all as gastritis? We do not think so. Often small hemorrhages and pigment spots are found in an otherwise normal and smooth mucous membrane. One of us (R. S.) published pictures of these conditions as early as 1923 and regards these findings as purely circulatory changes to be differentiated sharply from the lesions of chronic gastritis. We deem it necessary to designate as gastritis the changes of the mucous membrane associated with swelling, exudation or atrophy. Complete atrophy cannot properly be designated as inflammation, but since it is probably the end-result, it is so classified. The atrophy of the mucous membrane in pernicious anemia, however, may be of degenerative rather than of inflammatory origin.

We do not include chronic benign ulcer in the description of chronic gastritis—in contrast to the classification of Konjetzny, who by the demonstration of gastritis ulcerosa macroscopically and microscopically in the antrum of all stomachs on which resection had been performed for chronic ulcer convinced many investigators of the gastric origin of ulcer. Briefly stated, we find many such ulcers without inflammation of any kind, gastritis of the antrum is rarely seen in association with chronic gastric ulcer, though it occurs in association with duodenal ulcer with obstruction and retention, hemorrhages and pigment spots are often seen in a normal mucosa along the lesser curvature between the angle and the cardia in association with chronic benign gastric ulcer, a small erosion may be observed in the center of one of these hemorrhagic spots, and less often the ulcer itself lies within a hemorrhagic area, but hypertrophic changes may be seen commonly in the immediate neighborhood and rarely at a distance from the ulcer. Further discussion of this question will not be undertaken in this paper.

#### GASTROSCOPIC FINDINGS AND CLASSIFICATION

The numerous inflammatory changes, as seen with the gastroscope, permit different classifications. We prefer to subdivide chronic gastritis into three forms—superficial, atrophic and hypertrophic—because the morphologic observations are differentiated by gastroscopic examination and because this classification is clinically distinctly useful. One of us (R. S.) has found by repeated gastroscopic examinations for a period of years in cases in which treatment was given and in cases in which it was not that these forms, when there is no complication with specific etiologic agents, such as operation on the stomach, seem to run different courses, and therefore when they are first recognized they at once offer different prognoses.

CLASSIFICATION ON THE BASIS OF DIFFERENCES IN THE  
COURSE AND PROGNOSIS

## FORMS OF CHRONIC GASTRITIS

*Superficial Gastritis*—In superficial gastritis the surface epithelium, normally transparently clear, may be cloudy and lose its high lights and may be spotted with red, in contrast to the normal uniform orange-red. Less often the entire mucous membrane appears purple. At times the high lights are exaggerated if the upper sheaths of the mucous membrane are mildly edematous. In such a mucous membrane one often finds quite superficial erosions, which are usually surrounded by deep red hemorrhagic halos. Small superficial hemorrhages are, likewise, frequent.

Peculiarly striking are the exudative manifestations. While the healthy stomach usually contains only small threads of white secretion, the stomach with superficial gastritis contains layers of adherent, glairy or white secretion or gray or gray-green dirty, stringy secretion between the folds. All these changes are more marked in the body of the stomach, they are less frequently noted on the lesser curvature and are usually, but not always, absent in the antrum.

*Atrophic Gastritis*—In atrophic gastritis the mucous membrane loses its bright orange-red (in spite of equal illumination and the absence of shadow) and becomes gray-green and at the same time apparently thin. These green spots are commonly round or oval. Often one sees bluish blood vessels through the mucosa. In contrast to the earlier statement of one of us (R. S.) and the present opinion of Henning, we are now convinced that blood vessels are not seen through the normal mucosa, except occasionally in the fornix near the cardia, where a single vein may be a normal finding. This condition usually remains stationary but rarely develops into diffuse general atrophy.

Total atrophy was first described by Henning. Since that time we have observed the condition in a number of cases. The entire mucous membrane is grayish pink, gray or grayish green. Heavy, prominent, branching blood vessels are seen through the thin mucosa, their blue branches occasionally showing fine, dark red anastomoses. Such a picture is extraordinarily striking. Small erosions and broad subepithelial hemorrhages may occur. Resorption of these hemorrhages occurs without pigment formation.

We have frequently observed atrophic and superficial gastritis simultaneously in the same patient. In fact, in agreement with the older conception of chronic gastritis, the superficial form may develop into the atrophic. Gutzeit observed that this change may occur very rapidly, and we have observed it in a number of instances, only the atrophic areas being found in later stages.



*Hypertrophic Gastritis*—The chief gastroscopic finding in hypertrophic gastritis is swelling of the mucous membrane. The lining becomes velvet-like and flabby. Delicate crevasses develop, by means of which the mucosa is laid into polygonal plaques. Early these are most marked in the grooves but may involve the folds, causing them to become wider and stiffer in appearance than the normal. Abnormally rigid small folds may occur, which may be distinguished especially on the anterior portion of the gastric wall. Small warts and nodules occur, which are particularly striking when they are present on the top of the folds. Eventually gross nodes and tumor-like pseudopolyps are formed. All these forms are pictured in the atlas published by one of us (R. S.) and have again been illustrated by Henning's beautiful photographs.

All these changes are often accompanied by mucous and submucous hemorrhages, which may be extreme. Notably, multiple erosions come and go, which are deeper than the lesions occurring in superficial gastritis and yet may be easily overlooked by the inexperienced observer. Radial folds, first described by one of us (R. S.), surround these ulcers (whether this is due to scar formation is uncertain). In contrast to Henning's observations, we saw such a "starlike" formation persist after the healing of the ulcers but later disappear. Many ulcerations appear aphthous-like. Moutier (and after him, Korbsch) mentioned gastritis aphthosa. All changes occur much more frequently in the corpus than in the antrum but are observed in the latter region as well. The declaration made by one of us (R. S.) in 1923 that this disease involves chiefly the antrum can no longer be substantiated.

*Gastritis Following Operation on the Stomach*—Gastritis following operation on the stomach was first described by one of us (R. S.) in 1922 and has been observed later by every gastroscopist. Clairmont was the first surgeon to agree with the diagnosis. The condition is observed often in stomachs of the type in which the new opening does not show a rhythmic adaptation similar to that of the pylorus. It occurs as frequently in stomachs after resection as in stomachs on which gastroenterostomy has been performed. All the authors agreed that changes of all kinds are seen. Superficial, hypertrophic and, rarely, atrophic inflammation may be found. These changes are as marked as they ever appear. Sometimes the inflammation is restricted to the area surrounding the new opening, in other cases the whole stomach is inflamed. Erosions and hemorrhages are frequent.

#### COURSE AND PROGNOSIS OF THE DIFFERENT FORMS OF CHRONIC GASTRITIS

*Superficial Gastritis*—If one makes frequent gastroscopic observations on patients presenting conditions described as superficial gastritis, one notes a characteristic course of the disease. With carefully con-

trolled diet and lavage and possibly even with rest in bed, this disease heals completely and does not recur

We have not noted spontaneous healing in such cases, although the possibility must be admitted. Neither does the condition remain stationary if untreated. As already stated, frank atrophic gastritis develops

*Atrophic Gastritis*—In this form atrophic patches in an otherwise normal mucosa and also complete atrophy must generally be considered the end-stage. The localized patches may remain stationary, or they may increase in size and finally develop into large atrophic areas. This development may stop at any moment with adequate treatment. The patient suffers much less than a patient with hypertrophic gastritis. He is generally able to work and enjoy life, if he is careful to follow a proper diet. The mucosa, however, does not become normal again, and the atrophy persists. For this reason the prognosis of the atrophic form is also poor.

Atrophic gastritis has been regarded as the forerunner of carcinoma (Konjetzny, Huist, Moutier and one of us [R. S.])

In pernicious anemia, liver treatment seems to cause unexpected changes in the atrophic mucous membrane. Our observations on this point are not yet certain.

*Hypertrophic Gastritis*—The gastroscopist needs only to observe the patient with hypertrophic gastritis for years to learn how serious is this disease, how frequently hemorrhages recur, how poor is the prognosis for healing and how extremely rare is the development into atrophic gastritis.

In his experience one of us (R. S.) has seen no patient whom he was able to observe for a long period regain complete health. Abnormal gastroscopic findings persist. On the whole, patients with this condition suffer more than patients with chronic benign ulcer. In exacerbations of distress gastroscopic examination often discloses in the hypertrophic mucous membrane single or multiple ulcerations, which are not as deep as the chronic benign ulcer, present no niche and appear and disappear more quickly, healing of these erosions being a matter of days, not weeks. Even we, who criticize the use of purely descriptive terms, such as gastritis polyposa, gastritis verrucosa and gastritis granulosa, because they have little clinical significance at present, are tempted to use the term gastritis chronica hypertrophicans ulcerosa in these cases of clinical exacerbation of hypertrophic gastritis accompanied by multiple erosions.

Chronic hypertrophic gastritis does not heal with the ordinary gastric therapeutic measures, in spite of prolonged careful treatment. In one case of a severe form of the disease, in which all the usual treatments

were tried and sixty-five gastrosopic examinations were made over a period of ten years, high voltage roentgen therapy succeeded finally in rendering the mucous membrane normal and in eliminating the erosions, which had been present at all previous examinations. One year later, the mucous membrane became atrophic, apparently as a late consequence of the use of roentgen radiation.

*Gastritis Following Operation on the Stomach*—In inflammation of the stomach on which operation has been performed the prognosis is poor. Even the superficial forms do not heal. Recently we observed a case of jejunal ulcer in association with extremely severe gastritis following resection of the stomach in which the two diseases healed completely with treatment.

We have tried to emphasize why we prefer our classification to one of greater detail and why we do not place in one group all gastritides in which erosions occur or into another all the hemorrhagic varieties. Prognosis depends much more on the depth and type of changes in the mucosa and submucosa, which actually distinguish the three varieties, than on hemorrhages, which may occur in all three varieties, or on erosions, which heal and recur. Naturally, this conclusion has not been reached as a result of one observation on each patient but by careful observation of the course of the disease for years in a number of patients. One of us (R. S.) made sixty-five observations on one patient. That three or four observations on one patient are not enough on which to base a real opinion concerning his disease is certain. Infrequent observation is no doubt responsible for the differences of opinion existing among gastroscopists.

It is encouraging that Henning, who refused to adopt classification, accepted the aforementioned principle. He stated:

Even in regard to the making of a prognosis the triumph of morphologic diagnosis is evident. Not disturbance in function but the anatomic picture must be the basis of prognosis. For instance, the prognosis in cases of hypertrophic gastritis or of superficial changes will be judged more favorable for the return of gastric secretion than that in cases of diffuse atrophic gastritis, in which repair is no longer possible.

This is exactly what one of us (R. S.) thought to establish by his classification in 1922, except that he wished prognosis to depend not solely on the return of secretion but on the patient's ability to work and enjoy life, particularly with respect to whether treatment should be of long or short duration and, finally, on threatened dangers. We believe, on the basis of the protocols in three hundred and forty-six cases of chronic gastritis and the observations in three times that number of cases, that such a prognosis is possible on the grounds of the morphologic gastrosopic diagnosis. Investigations may eventually dem-

onstrate whether or not this classification can be related to a more exact knowledge of etiology<sup>1</sup>

#### OTHER CLASSIFICATIONS ON THE BASIS OF THE GASTRO-SCOPIC PICTURE

Moutier proposed a classification on the basis of strict anatomico-pathologic observations. This has the great advantage of the requirement of exact observation and interpretation by the gastroscopist. Moutier outlined the following scheme, derived from the study of seventy-three cases of chronic gastritis in his series.

It is obvious that such a detailed classification is more useful for the understanding of the disease, its type and severity, than the mere diagnosis of chronic gastritis, which Gutzeit preferred, but for the time

TABLE 1—*Classification of Seventy-Three Cases of Chronic Gastritis*

Type	Number of Cases	
Proliferative gastritis		33
Myxorrhoeal	7	
Hypertrophic	26	
Verrucous	23	
Tumor like	3	
Atrophic gastritis		28
Edematous and congestive	7	
Hemorrhagic	1	
Erosive	8	
Ulceromembranous or aphthous	5	
Ulcerous	5	
Necrotic	2	
Atrophic gastritis		2
Generalized	1	
Localized	1	
Gastritis of mixed nature		10
Generalized	3	
Segmental (lesser curvature)	7	

being it seems to us to offer no great usefulness, for the single lesions in these conditions intermingle so markedly, come or go repeatedly in the same patient and have in the superficial and atrophic types of gastritis (for instance, in the case of erosion or hemorrhage) so different a prognosis from that of similar lesions occurring on a hypertrophic base. Perhaps in the future, by such a detailed classification as that of

1 The excellent book of Faber entitled "Gastritis and Its Consequences" appeared since the completion of this paper, and therefore we cannot incorporate a detailed discussion of it, but the classification of Faber is essentially the same as ours. He encountered anatomically "two distinct forms," namely, "chronic erosive gastritis" and "gastritis progressiva atrophicans." It is apparent from his description that his first group corresponds with our group of "hypertrophic gastritis" and that the second group contains our forms "superficial" and "atrophic" gastritis. The anatomist believes that atrophy rather than healing is the end-result of superficial gastritis. This can be determined only by repeated gastroscopic observations. Therefore we distinguish between superficial and atrophic gastritis, although we admit a certain relationship.

Moutier, one may, after observing the course of various forms in a large number of cases, eventually establish specific disease pictures which are as diagnostic as the pictures of mercurial stomatitis or Vincent's angina

Gutzeit, as already mentioned, rejected every kind of subdivision, contending that in each case a variety of changes indistinguishable by gastrosopic examination are present. Henning, however, expressed the belief that generally one form prevails. We agree with Kalk, who stated that orderly arrangement and subdivision of the multitude of pictures are indispensable.

### SYMPTOMATOLOGIC CLASSIFICATION

All authors who have made gastrosopic examination in many cases of chronic gastritis have agreed that the symptomatology is so vague that neither diagnosis nor classification on a symptomatologic basis is possible.

Patients suffering from chronic gastritis complain of a variety of digestive symptoms. Severe pain occurs, especially when erosions are present and hemorrhages develop in an atrophic mucous membrane. For months slight lack of appetite in association with slight sense of pressure in the epigastrium may accompany the disease, the course of which is interrupted by exacerbations, with inability to work.

Kalk suggested that the localization of lesions in chronic gastritis may have an influence on the type of symptoms. We prefer to discuss these problems in a later paper. We wish at this time to state only that in our opinion diagnosis and classification of chronic gastritis on the basis of symptoms are impossible. This is unfortunate, for the general practitioner naturally wishes to make such an important diagnosis without the use of complicated diagnostic methods. This desire, though justified, cannot change the facts.

### VALUE OF THE ROENTGEN RELIEF METHOD FOR DIAGNOSIS AND CLASSIFICATION

The width of the fold, whether greater than normal, on the one hand, or less than normal, on the other, as outlined by means of barium sulfate compression, has been assumed to distinguish between hypertrophic and atrophic gastritis. It is our experience that diagnosis on the basis of these roentgen examinations cannot be depended on. There appears to be no correlation between the size of the folds seen in relief on roentgen examination and the actual thickness of the mucosa. The longer gastroscopists (Henning, Gutzeit, Maley and one of us R. S.) have compared their findings with observations with the roentgen relief method the more they have dissented from the opinion of certain roent-

genologists that the width of the folds as outlined by barium can give any definite information about the width of the actual mucosal folds and the pathologic condition of the mucous membrane. By the relief method a diagnosis of rigid thickened folds has been made in cases in which complete atrophy was found by gastroscopic examination, or in which pernicious anemia was present (Arafa, Henning and Levine and Ladd), and, on the contrary, no abnormal roentgen observations have been made in cases in which the most marked changes were seen gastroscopically.

Henning has published the table presented as table 2, in which the roentgenologic appearance of the folds is compared with the gastroscopic findings.

TABLE 2—*Comparison of the Roentgenologic and Gastroscopic Findings in Cases of Chronic Gastritis (After Henning [Deutsche med Wchnschr 60 1455, 1934])*

Roentgenologic Appearance of Folds	Diagnosis on Basis of Gastroscopic Findings
Broad	Hypertrophic gastritis Erosive gastritis Atrophic gastritis Normal mucosa
Normal	Normal mucosa Hypertrophic gastritis Atrophic gastritis Erosive gastritis
Narrow	Normal mucosa Atrophic gastritis

It is not denied that in rare instances roentgenographic and gastroscopic findings agree. It is obvious that this will be so in the occasional case in which the gross changes due to gastritis result in isolated, very stiff and thickened folds or in cases of gross mucosal hyperplasia, the latter condition producing the typical corn-cob roentgen relief picture, which resembles polyposis but shows smaller negative shadows. In 1926, prior to the reports of Berg, Gutzeit and Cole, two American authors, Brunn and Pearl, demonstrated such a picture. The roentgenographic method on the whole, in our experience, is unreliable for the diagnosis of chronic gastritis.

#### VALUE OF LABORATORY FINDINGS

It has long been attempted to diagnose gastric disease by chemical, quantitative, qualitative and microscopic examinations of the gastric content. The difficulty of this means is clear even in such well established diseases as carcinoma and ulcer, in which the secretion, the amount of the content and the results of chemical and microscopic tests may point the way but are never truly diagnostic. This is equally true in chronic gastritis. It was thought for a time that the number of cells in the gastric juice might be of aid, but the kind and number varied to

such a degree that the method seems to us unreliable, though Westphal consistently continues to use it. The reaction to the aldehyde test is, in our experience, often positive in cases of superficial gastritis.

Even in atrophic gastritis, which is generally believed to be accompanied by functional achlorhydria, the previously expressed opinions of Henning, Moutier, Gutzeit, one of us (R. S.) and other gastroscopists are contradicted. Of fourteen cases in which there were localized areas of atrophy, observed in the Albert Merritt Billings Hospital, the values for free acid were between 26 and 52 in seven and below 23 in three, and only in four instances was there no free hydrochloric acid with the Ewald and histamine tests.

### ETIOLOGIC CLASSIFICATION

Classification of morphologic changes on the basis of etiologic factors is usually fruitful, because therapeutic indications become clear thereby, but, as we shall attempt to show, so little is yet known definitely about chronic gastritis that such a classification is not practicable. The following agents may act as etiologic factors:

*Acute Gastritis*—In general, it is conceivable that any form of chronic gastritis, including atrophy, may develop from acute gastritis due to any exogenous cause. We, however, have observed only the superficial variety to result.

*Mechanical Factors*—It is hardly to be doubted that constant exogenous trauma is a cause of chronic gastritis. Mechanical factors are certain causes, as is evident from the famous work of Beaumont one hundred years ago. Hypertrophic gastritis, so often present in association with pyloric stenosis, may be of mechanical origin.

*Chemical or Toxic Factors*—Alcohol, nicotine and perhaps certain drugs (such as salicylates) apparently may be real causes, usually of superficial gastritis.

*Infectious Agents*—Chronic infection of the tonsils or sinuses may conceivably act as foci or may deliver infectious material into the stomach.

*Excretory Agents*—Chronic gastritis due to excretion is often present in cases of lead poisoning. Gutzeit observed hypertrophic and atrophic changes and ulcerations. Possibly the gastritis occurring in chronic nephritis is due to the excretion of toxins.

*Bacteria and Protozoa*—Acute gastritis may be due to the bacterial toxins of infectious disease. Whether acute gastritis ever develops into the chronic form has not been observed gastroscopically. Aside from the specific granulomas, such as the lesions occurring in syphilis, tuberculosis and anthrax, the bacterial origin of chronic gastritis is not established. Henning was skeptical of the observation even of hemo-

lytic streptococci. In the experience of one of us (R S), lambliosis of the duodenum is accompanied by superficial gastritis, which disappears when the organisms are killed by arsphenamine.

*Various Etiologic Factors in Atrophic Gastritis*—As previously stated, atrophic gastritis may be regarded as purely degenerative rather than as primarily inflammatory, as, for instance, cases of pernicious anemia or in the other cases in which only atrophy is seen. Localized atrophy occurs (1) without known cause, (2) occasionally in association with pernicious anemia, (3) in superficial gastritis, (4) in bacillary dysentery and (5) in sprue while total atrophy was seen when the cause was unknown, in cases of pernicious anemia and of superficial gastritis and in association with carcinoma and benign tumor. Konjetzny, Hurst and others were agreed that in cases of carcinoma and benign tumor the atrophy is primary. In the Billings Hospital we observed a striking case of combined degeneration of the cord in which the blood findings characteristic of pernicious anemia were absent but total atrophy of the mucous membrane was present. It may be seen from the preceding sketchy discussion that the etiology of chronic gastritis is far from clear. When it is determined it will presumably be the most satisfactory means of classification.

#### CONCLUSIONS

- 1 Chronic gastritis is the most frequent disease of the stomach
- 2 Gastroscoy is the best method of diagnosis at present
- 3 Chronic gastritis should be classified as (a) superficial gastritis, (b) atrophic gastritis, (c) hypertrophic gastritis and (d) gastritis following operation on the stomach
- 4 These four types differ markedly in their course and prognosis
- 5 A classification of chronic gastritis on the basis of symptomatology or etiology is at present impossible
- 6 Roentgenographic and laboratory methods are not substitutes for gastroscoy examination

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# ROENTGENOLOGIC OBSERVATIONS ON VARIOUS TYPES OF CHRONIC ARTHRITIS

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Although numerous reports have been published on the roentgenologic observations on various forms of chronic arthritis, the subject has not received the careful attention which it merits from the point of view of differential diagnosis. A considerable number of the studies which have been reported have dealt with the question of tuberculous and pyogenic arthritis, and comparatively little attention has been paid to the much more frequent rheumatoid arthritis and osteo-arthritis. In recent years, however, the increasing tendency to regard rheumatoid arthritis and osteo-arthritis as separate and distinct clinical entities has focused attention on these two varieties of arthritis, and there have been reports of several studies dealing with the roentgenologic observations on the two diseases.<sup>1</sup> The student of arthritis is particularly referred to the recent comprehensive work of Brailsford,<sup>1d</sup> with its extensive bibliography.

At the arthritis clinic of the Presbyterian Hospital and at the New York Orthopedic Dispensary and Hospital an effort has been made to correlate the clinical and roentgenologic observations on various forms of chronic arthritis, and in the course of the investigation particular consideration has been given to the changes observed in rheumatoid arthritis and osteo-arthritis. The roentgen observations on other common forms of chronic arthritis have also been studied and are described in the present report.

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1 (a) Allison, N, and Ghormley, R K. *Diagnosis in Joint Disease*, New York, William Wood & Company, 1931. (b) Scott, S G. *Brit M J* **1** 275, 1932. (c) Rigler, L G, and Wetherby, M. *Am J Roentgenol* **29** 766, 1933. (d) Brailsford, J F. *The Radiology of Bones and Joints*, Baltimore, William Wood & Company, 1934.



From a total of 300 cases observed in detail, a representative number of each of the more common varieties of chronic arthritis has been selected. These cases were chosen because clinical and laboratory findings were characteristic of the type of arthritis represented. The groups studied were as follows: (1) rheumatoid arthritis, 59 cases, (2) osteoarthritis, 32 cases, (3) gout, 12 cases, (4) gonococcic arthritis, 11 cases, (5) tuberculous arthritis, 32 cases, (6) rheumatoid spondylitis (Marie-Stumpell), 11 cases, and (7) Still's disease, 11 cases.

#### CLINICAL OBSERVATIONS

The diagnostic criteria employed in classifying the various forms of chronic arthritis are well established in the minds of the majority of observers. This is certainly true so far as gout and gonococcic and tuberculous arthritis are concerned. Some confusion still exists in regard to rheumatoid arthritis and osteoarthritis, but there is an increasing tendency to separate these forms of chronic arthritis into sharply defined clinical types. In the present study rheumatoid arthritis and osteoarthritis have been considered as separate clinical entities. The differentiation has been based on the early observations of Garrod<sup>2</sup> and Nichols and Richardson<sup>3</sup> and the more recent studies of other investigators.<sup>4</sup> The clinical and laboratory observations in cases of various forms of arthritis are summarized in the following section.

*Rheumatoid Arthritis*—All the patients with a diagnosis of rheumatoid arthritis presented the classic appearance of patients suffering from this disease. The majority showed typical fusiform swellings or contracture deformities, and many had subcutaneous nodules.<sup>5</sup> They were apparently the victims of a chronic infectious process and showed a consistently high sedimentation rate, with an average of 50 mm. in one hour.<sup>1b</sup> The serum of the majority (43) of the patients definitely agglutinated hemolytic streptococci,<sup>6</sup> the serum of 2 of the remaining 9 failed to agglutinate, and for 7 the agglutination titer was not determined. The ages of the patients ranged from 22 to 72 years, the average being 49 years. The symptoms varied in duration from two months to eighteen years, with an average of five years.

*Osteoarthritis*—The condition in the cases of osteoarthritis was typical of the degenerative form of arthritis. Many patients had Heberden's nodes. The majority

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2 Garrod, A. E. *Rheumatoid Arthritis, Osteo-Arthritis*, in Albutt, C., and Rolleston, H. D. *A System of Medicine*, New York, The Macmillan Company, 1909.

3 Nichols, E. H., and Richardson, F. L. *J. M. Research* **21** 149, 1909.

4 (a) Cecil, R. L. *The Diagnosis and Treatment of Arthritis*, in Christiar, H. A. *Oxford Monographs on Diagnosis and Treatment*, New York, Oxford University Press, 1929, vol. 6. (b) Dawson, M. H., Sia, R. H. P., and Boots, R. H. *J. Lab. & Clin. Med.* **15** 1065, 1930.

5 Dawson, M. H. *J. Exper. Med.* **57** 845, 1933.

6 Dawson, M. H., Olmstead, M., and Boots, R. H. *J. Immunol.* **23** 187 and 205, 1932.

were overweight and had comparatively mild symptoms, involving chiefly the larger, weight-bearing joints. There was little or no evidence of infection, the sedimentation rates were low, with an average of 19 mm in one hour, and in no instance was there definite agglutination with *Streptococcus haemolyticus*. The age of the patients varied from 32 to 65 years, the average being 53 years. The symptoms had persisted from one to thirty-six years.

*Gout*—All the patients with gout gave a history of recurrent paroxysmal attacks involving one or more of the small joints. Several showed tophi, and all had high values for uric acid in the blood, with an average of 6.1 mg per hundred cubic centimeters. The ages of the patients varied from 34 to 74 years, with an average of 54 years.

*Gonococcic Arthritis*—All the patients with gonococcic arthritis had a urogenital infection, and in 73 per cent of the cases the diagnosis was substantiated either by a positive culture or by a positive reaction in the complement-fixation test. All the patients except 1 presented monarticular involvement after the first few days of pains in several joints. The ages of the patients varied from 20 to 36 years, and the symptoms had persisted from four weeks to four months.

*Tuberculous Arthritis*—The patients with tuberculous arthritis presented characteristic, slowly progressive symptoms, and all but 3 of the 32 patients showed monarticular involvement. The diagnosis was verified in most cases by inoculation of guinea-pigs or by histologic study of sections of tissue obtained at operation for fusion (20 cases) or for drainage (2 cases). The ages of the patients varied from 7 months to 67 years, and the symptoms had persisted from one month to forty-six years.

*Rheumatoid Spondylitis (Marie-Strumpell)*—The patients with rheumatoid spondylitis showed a definite ankylosing type of spondylitis, with a tendency to poker spine and round back deformity. Only 1 patient had symptoms in the peripheral joints of the extremities. The serum of only 1 patient showed definite agglutination with hemolytic streptococci, although the serum of 6 patients was reported as giving a doubtful reaction. The sedimentation rate was consistently above normal, ranging from 30 to 79 mm in one hour. The ages of the patients varied from 21 to 42 years, and the symptoms were present for from two to twelve years.

*Still's Disease*—The children with Still's disease presented characteristic fusiform swelling of the fingers or contracture deformities. The majority of patients showed evidence of chronic focal infection. As was expected in this younger age group, agglutination of the serum with hemolytic streptococci was not well marked,<sup>6</sup> although the serum of 1 patient gave a positive reaction (1:160) and the reactions of the serum of 4 were reported doubtful. The sedimentation rate was elevated in the majority of cases, the average being 51 mm in one hour.

#### ROENTGENOLOGIC OBSERVATIONS

*Definition of Roentgenologic Terms*—In presenting the roentgenologic observations on various forms of chronic arthritis, it is emphasized that this report is only preliminary. During the investigation the roentgenologists (A, B, F, and H, K) were not given any clinical information concerning the patients except the duration of the symptoms and the degree of function or immobility of the joints. Their observations were recorded separately on a chart listing fifteen chief items, with

forty-nine detailed descriptive roentgenologic subdivisions. Six of the more outstanding items are discussed in this report and may be described as follows:

1 **Decalcification** Decalcification is a decrease in the density of bone without loss of architecture. Three types are recognized, depending on the extent and distribution of the process:

(a) Systemic decalcification refers to the type that occurs throughout the entire skeleton. It occurs normally to a slight degree in persons in middle and in old age, but it is most characteristically observed in persons with rheumatoid arthritis.

(b) Regional decalcification is the form that involves a particular area in the body, for example, one of the extremities. The picture is similar to that observed in cases of atrophy of disuse, and as a rule all the bones shown on any one film are involved.

(c) Local decalcification is a decrease in the density of bone confined to a circumscribed area, for example, the neighborhood of one particular joint.

2 **Production of Bone** (a) Lipping refers to a calcareous deposit at the articular margin. The deposit is small and pointed, and there is a tendency to conform to the outline of the adjacent soft tissues. (b) Osteophytes are larger calcareous deposits, which are more irregular and exuberant. They often occur in ligamentous structures.

3 **Destruction of Bone (Loss of Bone Substance)** This is the term applied to a localized area of complete loss of calcium and bone architecture. Two varieties are recognized and require further definition:

(a) Active destruction of bone is indicated by a spiculed and irregular margin of the remaining bone, by a decrease in the density of calcium in the surrounding area and by a tendency to progress as evidenced in repeated examinations.

(b) Atrophic destruction of bone is evidenced by the occurrence of smaller or larger rounded areas, which present a smooth, sharply punched-out appearance. Such areas can be recognized only at the margin of bone usually at or near the joint. These areas stand out in sharp contrast to the bone, and there is no decrease in the density of calcium in the surrounding bone. These punched-out areas were formerly ascribed chiefly to gout.

4 **Joint Space** This is the area between the articular surfaces of contiguous bones which is normally occupied by cartilage. The area may be narrowed or obliterated (or at times even widened), according to the degree of destruction present in the articular cartilage.

5 **Ankylosis** This process occurs at the site of destroyed cartilage and may be of two types:

(a) Bony ankylosis is identified by continuous trabeculae of bone extending from bone end to bone end. The change may occur in joints which are essentially immovable, for example, in the sacro-iliac joints, or in other joints that have had previous damage to the cartilage.

(b) Fibrous ankylosis can be estimated only from the roentgenograms. It is evidenced by the absence of a joint space when bony ankylosis is not present.

6 **Changes in the Soft Tissues** In the present study considerable attention has been paid to the appearance and nature of the shadows made by the soft tissues. In spite of the fact that they may yield information of the greatest value, these

shadows are frequently overlooked in the routine examination of films of joints. In particular, observations have been made on the degree of atrophy or swelling in the periarticular tissues and on the nature and character of the effusion into the joint. The terms may be defined as follows:

(a) Atrophy is indicated by a decrease in the diameter of the shadows made by the soft tissues. If the process is confined to one extremity, the degree of atrophy can be readily determined by comparison with a roentgenogram of the uninvolved extremity, if the process is bilateral, the degree of atrophy can only be estimated.

### RHEUMATOID ARTHRITIS

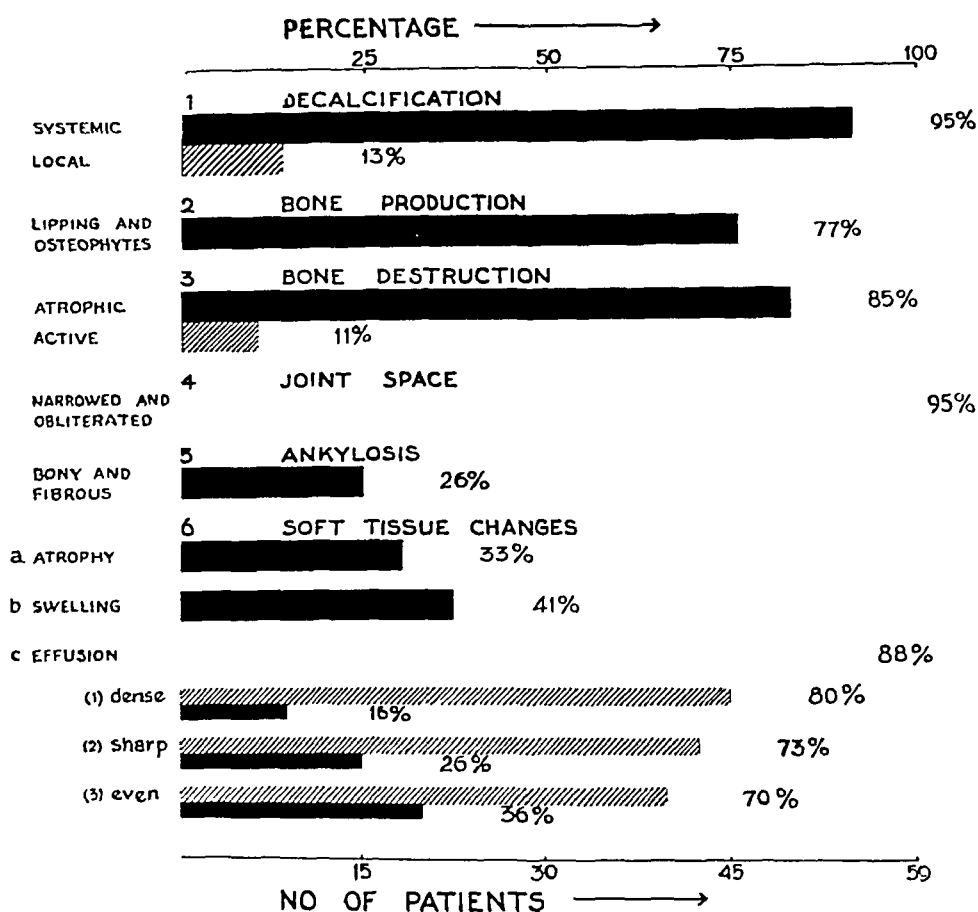


Fig 1—Observations on patients with rheumatoid arthritis

(b) Swelling is indicated by an increase in the diameter of the shadow of the soft tissues outside the joint capsule.

(c) Effusion is indicated by an increase in the diameter of the shadow of the soft tissues represented by the capsule and its contents. The capsule is usually outlined by the adjacent soft tissues, and the shadow cast by the effusion may vary greatly in its intensity, character and distribution. Thus, the shadow may be (1) dense or faint, (2) sharply defined or poorly defined and (3) evenly or unevenly distributed throughout the entire space enclosed by the joint capsule.

*Summary*—A tabulation of these six roentgenologic features, culled from the detailed observations, reveals a combination or grouping that

is characteristic for each of the seven types of chronic arthritis studied in this series. A summary of the observations on each of these types of arthritis follows. (The percentages refer to the incidence in relation to the number of cases studied.)

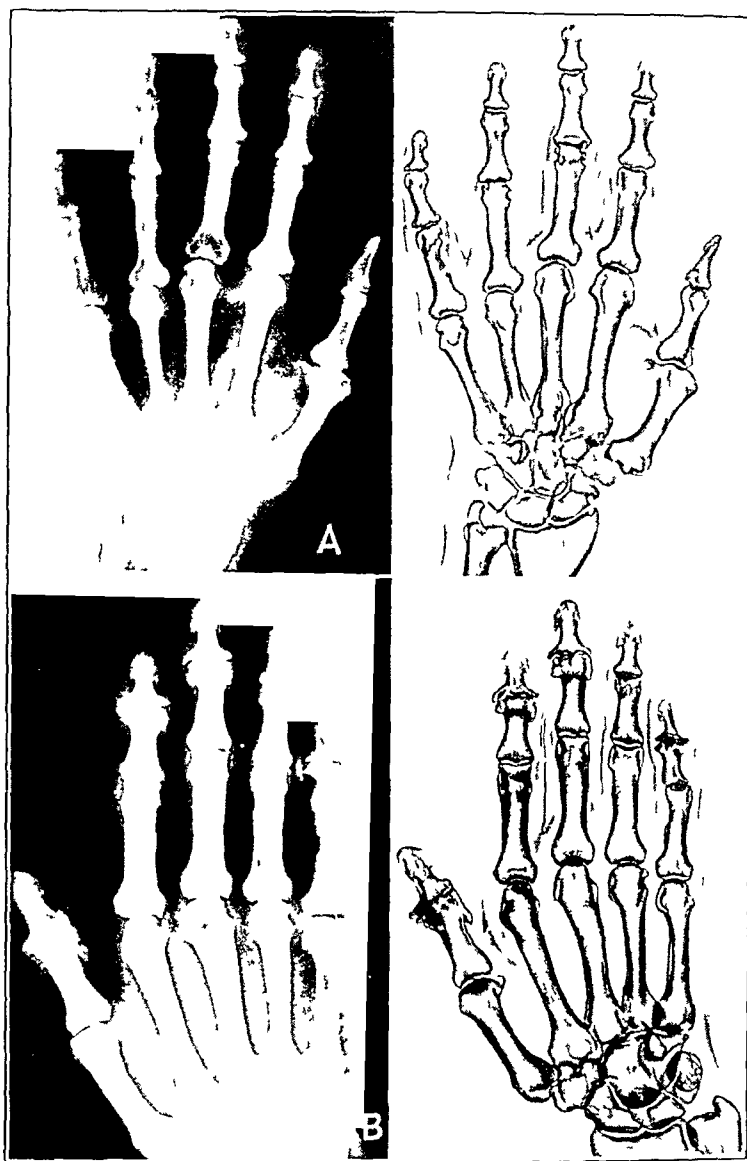


Fig 2—*A* is a roentgenogram and drawing of a patient with rheumatoid arthritis, showing systemic decalcification, small areas of atrophic destruction of bone, narrowing of the joint spaces, swelling of the soft tissues and effusion, which is symmetrical and especially well marked about the proximal interphalangeal joints. *B* is a roentgenogram and drawing of a patient with osteoarthritis, showing absence of decalcification, marked production of bone, especially at the terminal interphalangeal joints, and comparative absence of destruction of bone or changes in the soft tissues. Drawings of the roentgenograms have been made in order to emphasize the important roentgenologic features.

*Rheumatoid Arthritis* (Fig 1, 59 Patients, 207 Joints) —Marked systemic decalcification was present in 95 per cent of the cases. This systemic decalcification occurred throughout the skeleton, but it was best seen in the bones of the hands and feet.

Atrophic destruction of bone was noted in 85 per cent of the cases. This appearance, often referred to as punched-out areas, is a prominent

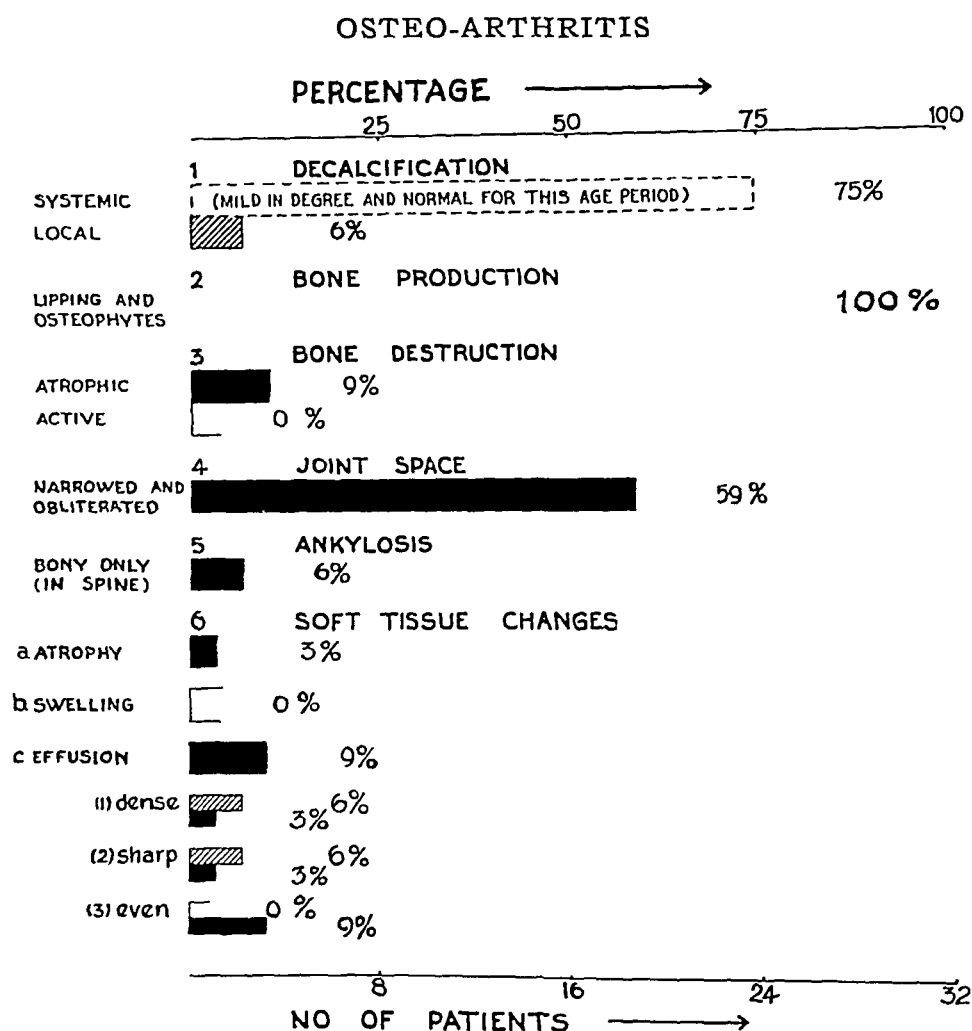


Fig 3—Observations on patients with osteo-arthritis

feature of rheumatoid arthritis and occurs as frequently in cases of this disease as in cases of gout. As a rule, however, the areas of atrophic destruction are smaller in rheumatoid arthritis than in gout.

Effusion is a characteristic feature of rheumatoid arthritis. In the majority of cases the shadow was dense (80 per cent), sharply outlined, fusiform (73 per cent) and evenly distributed (70 per cent).

There was a slight degree of atrophy of soft tissues (33 per cent) or swelling (41 per cent) or both. There was comparative absence of local decalcification (13 per cent) or active loss of bone substance (11

per cent) Destruction of cartilage, although prominent in rheumatoid arthritis, was not especially characteristic of the disease

Particular mention should be made of the large percentage (77) of patients with rheumatoid arthritis who showed production of bone (lipping and osteophytes) In the majority of cases it was possible to differentiate the general character of this change from that seen in cases

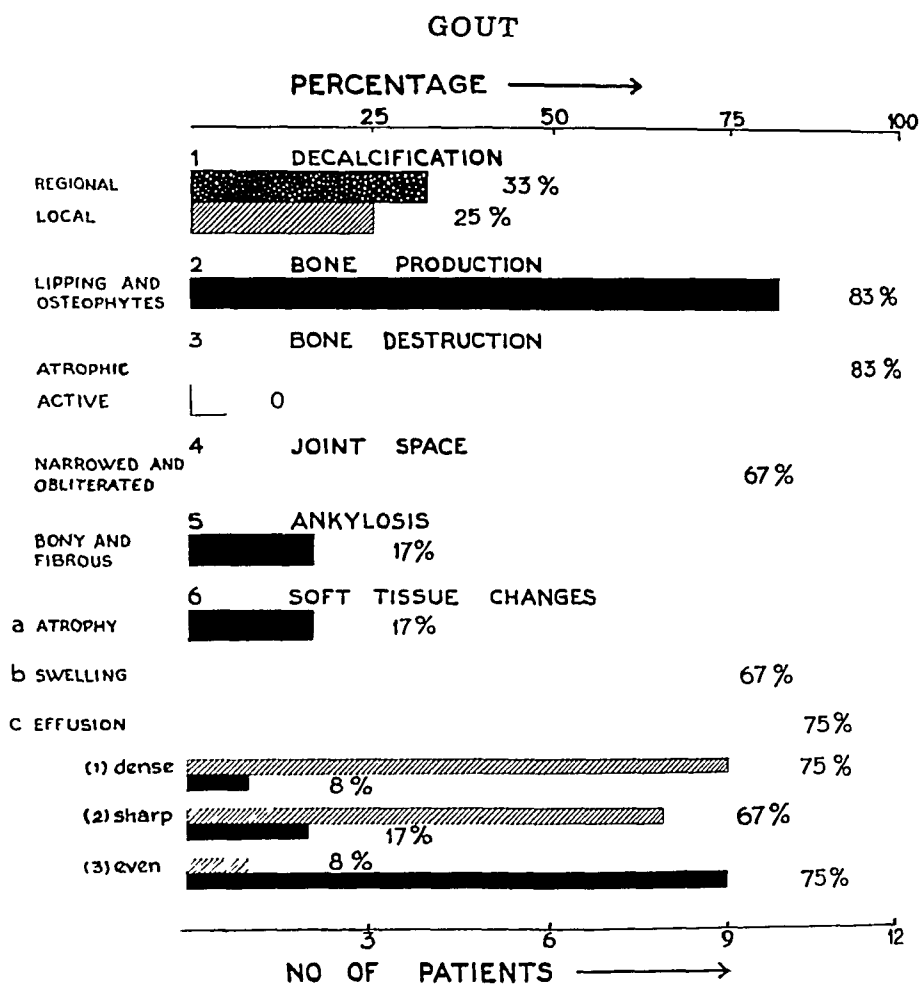


Fig 4—Observations on patients with gout

of true osteo-arthritis In certain patients, however, the characteristic appearances of rheumatoid arthritis and osteo-arthritis could be observed coexisting in the joint In view of the high incidence of osteo-arthritis in the population at large, especially in persons in the older age groups, this was not an unexpected finding and does not invalidate the conception that osteo-arthritis and rheumatoid arthritis are distinct entities

*Osteo-Arthritis* (Fig 3, 32 Patients, 52 Joints) —Marked production of bone, with lipping or osteophytes, was noted in all the cases (100 per cent)

Narrowing or obliteration of the joint space was present in 59 per cent of the cases. Narrowing of the joint space in cases of osteoarthritis was most frequently observed in weight-bearing joints and in the terminal interphalangeal joints of the hands. In the weight-bearing

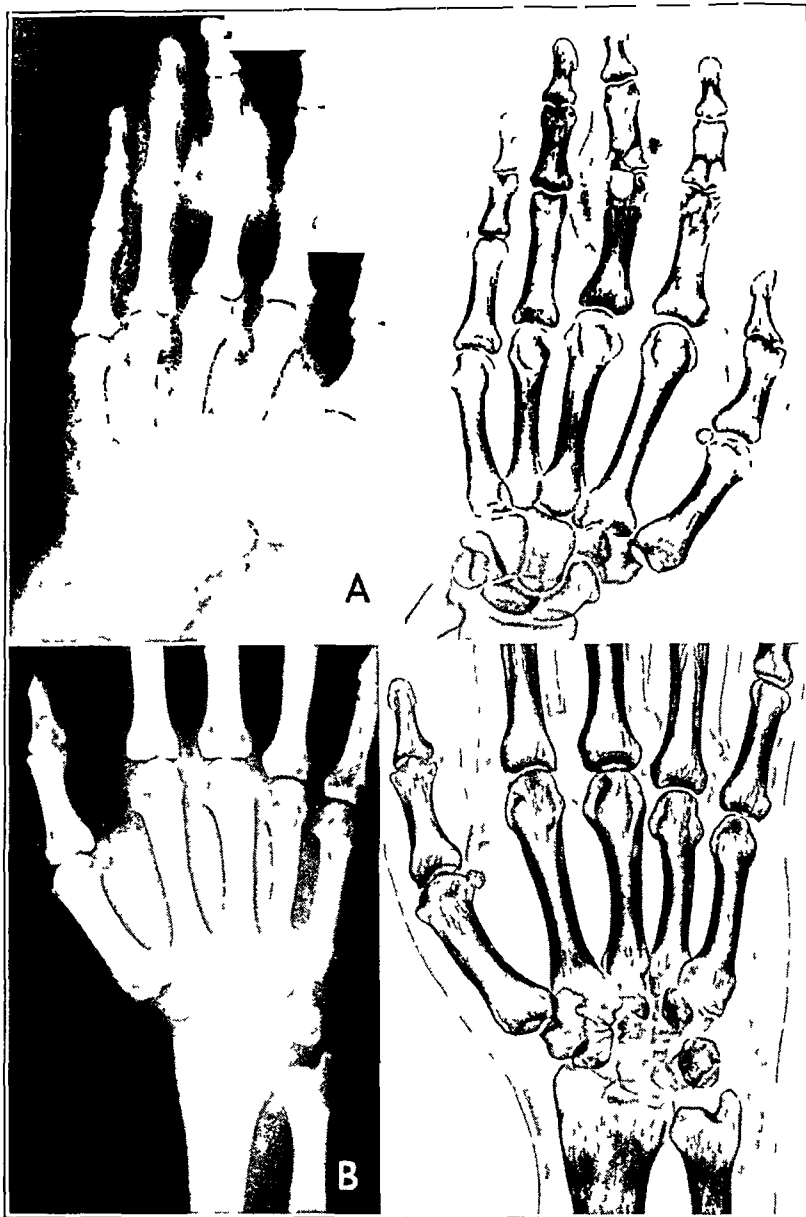


Fig 5—*A* is a roentgenogram and drawing of a patient with gout, showing large areas of atrophic destruction of bone and changes in the soft tissues centered on the areas of destruction of bone rather than on the joint itself. *B* is a roentgenogram and drawing of a patient with gonococcal arthritis in an early stage, showing local and regional decalcification, swelling of the soft tissues and effusion, active destruction of bone and narrowing and obliteration of the joint spaces.

joints, that portion of the joint subjected to the greatest degree of trauma showed the most marked involvement. The narrowing was due



to a more or less localized destruction of the articular cartilage and was frequently associated with sclerosis of the subarticular bone

There was seldom any destruction of bone (9 per cent) or change in the soft tissue (9 per cent). Bony ankylosis, except in the "half" joints of the spine or sacro-iliac joints, was rare, and its presence indicated previous destruction of the cartilage due to other factors, such as trauma or infection. A slight degree of systemic decalcification was noted in 75 per cent of the cases. However, it should be pointed out that this degree of systemic decalcification is essentially normal for persons in the age period and occurs independently of any arthritic involvement. It was considerably less than the degree of systemic decalcification noted in cases of rheumatoid arthritis.

*Gout* (Fig 4, 12 Patients, 21 Joints) —Swelling of the soft tissues was present in 67 per cent of the cases. The swelling was characteristically circumscribed, with fairly well defined borders, and was eccentric to the joint. Thus, since the swelling was not centered on the joint, there was not the symmetrical fusiform appearance seen in cases of rheumatoid arthritis.

Effusion was present in 75 per cent of the cases. The effusion was dense (75 per cent), sharply defined (67 per cent) and uneven (75 per cent) and was centered more on the area of atrophic destruction of bone than on the joint space. The character of the swelling and that of the effusion represent one of the most important differential points between gout and rheumatoid arthritis.

There was atrophic destruction of bone, or punched-out areas, in 83 per cent of the cases. These areas, although similar to those noted in cases of rheumatoid arthritis, were usually larger. There was some atrophy of soft tissues (17 per cent), the joint space was occasionally widened, and there was often a slight degree of regional (33 per cent) or local (25 per cent) decalcification.

*Gonococcic Arthritis* (Fig 6, 11 Patients, 12 Joints) —The roentgenologic features of gonococcic arthritis vary so markedly with the stage of the disease that it is necessary to differentiate between early and late changes.

In the early stage swelling of the soft tissue is usually marked, it appears early and subsides within a few days or a few weeks. Local decalcification was noted in 64 per cent of the cases, and slight effusion was present in 64 per cent. Both the local decalcification and the effusion decreased in the later stages of the disease.

In the later stages 82 per cent of the patients showed narrowing of the joint space, 36 per cent showed a moderate degree of active destruction of bone and 45 per cent showed comparatively early healing, with fibrous or bony ankylosis.

Patients who have had gonorrhea may show another type of lesion in the metatarsophalangeal joints. Each of these joints may be involved in a peculiar process, the essential feature of which is atrophic destruction of bone. Unlike the lesions observed in cases of rheumatoid arthritis, there is no evidence of effusion, swelling or repair. When these changes are observed in the metatarsophalangeal joints, calcaneal

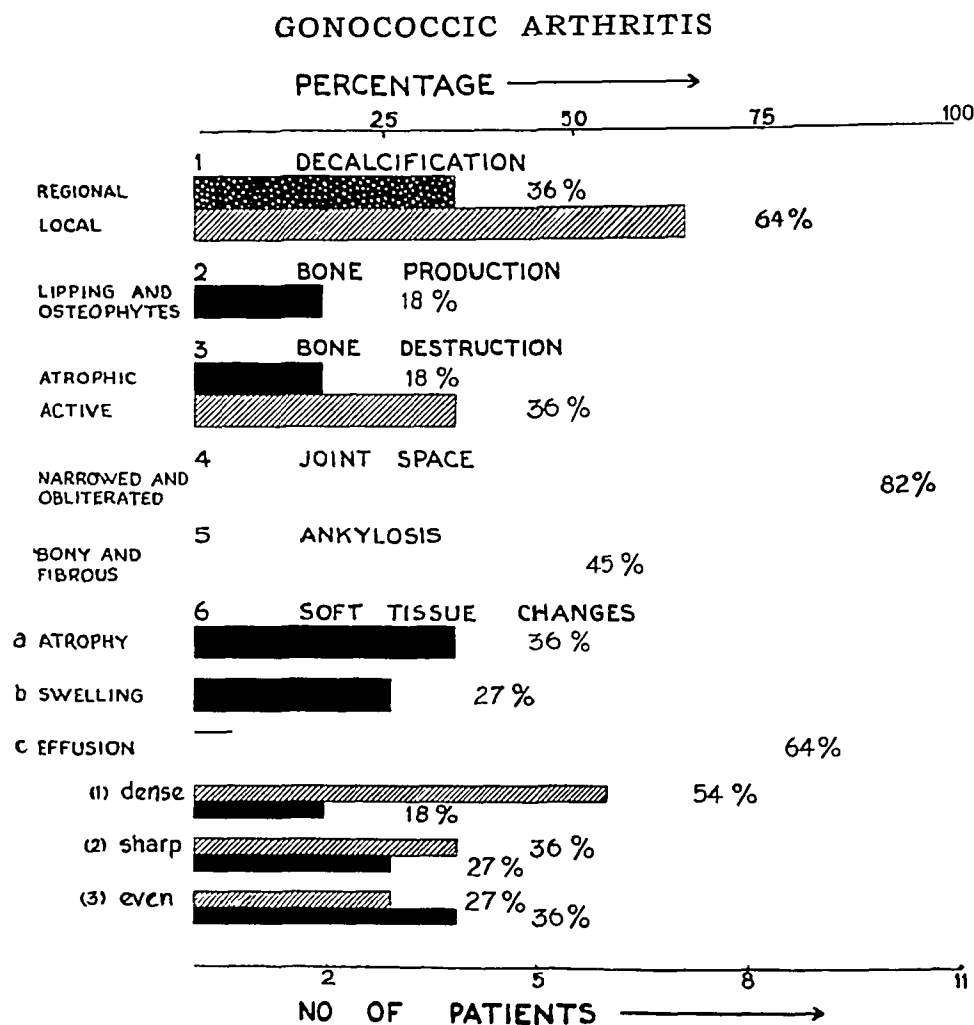


Fig 6—Observations on patients with gonococcic arthritis

spurs are usually present and are of the type associated with gonococcic infection. These spurs are irregular in outline and density and are less sharply defined against the soft tissues than the usual degenerative spurs of osteo-arthritis.

*Tuberculous Arthritis* (Fig 8, 32 Patients, 35 Joints) —Regional decalcification was present in 78 per cent of the cases, and local decalcification was noted in 72 per cent. Both the regional and the local decalcification persisted through the entire course of the disease.

Marked active destruction of bone was present in 84 per cent of the cases. This condition occurred early and tended to be slowly progressive, as was noted in roentgenograms made subsequently. There was atrophy of soft tissues in 66 per cent of the cases, and swelling

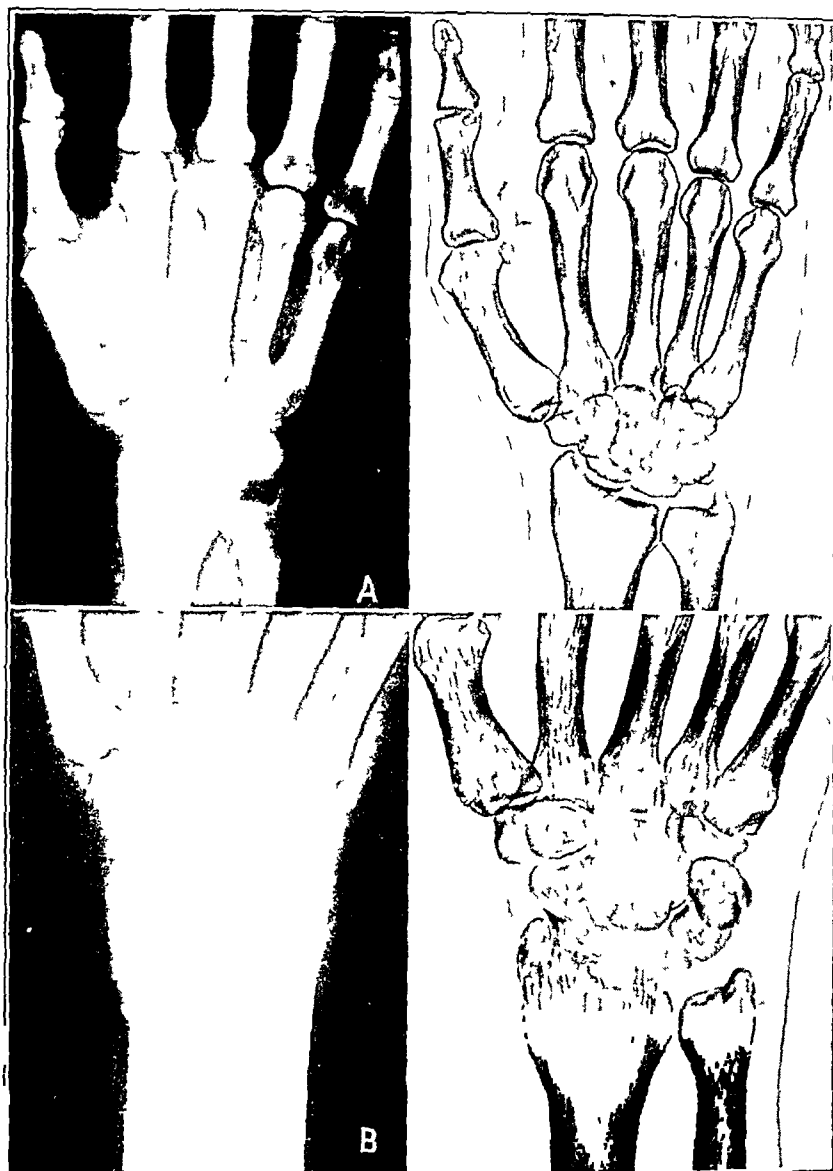


Fig 7—*A* is a roentgenogram and drawing of the patient with gonococcal arthritis observed in figure 5*B*, made seven months later. It shows fibrous and bony ankylosis and recalcification. *B* is a roentgenogram and drawing of a patient with tuberculous arthritis, showing local and regional decalcification, a marked degree of active destruction of bone, narrowing and obliteration of the joint spaces, swelling of the soft tissues and effusion.

in 70 per cent. Effusion was noted in 72 per cent. The effusion constantly persisted and was dense (66 per cent), sharp in outline (53 per cent) and evenly distributed (41 per cent).

In cases of tuberculous and gonococcic arthritis the duration and severity of the symptoms are of the greatest importance when one attempts to interpret the roentgen shadows in terms of pathologic processes in the joints. These two forms of arthritis possess several features in common, but the length of time required for the development of the changes in tuberculous arthritis is likely to be ten or twenty times as long as that required to produce the corresponding changes in gonococcic arthritis.

## TUBERCULOUS ARTHRITIS

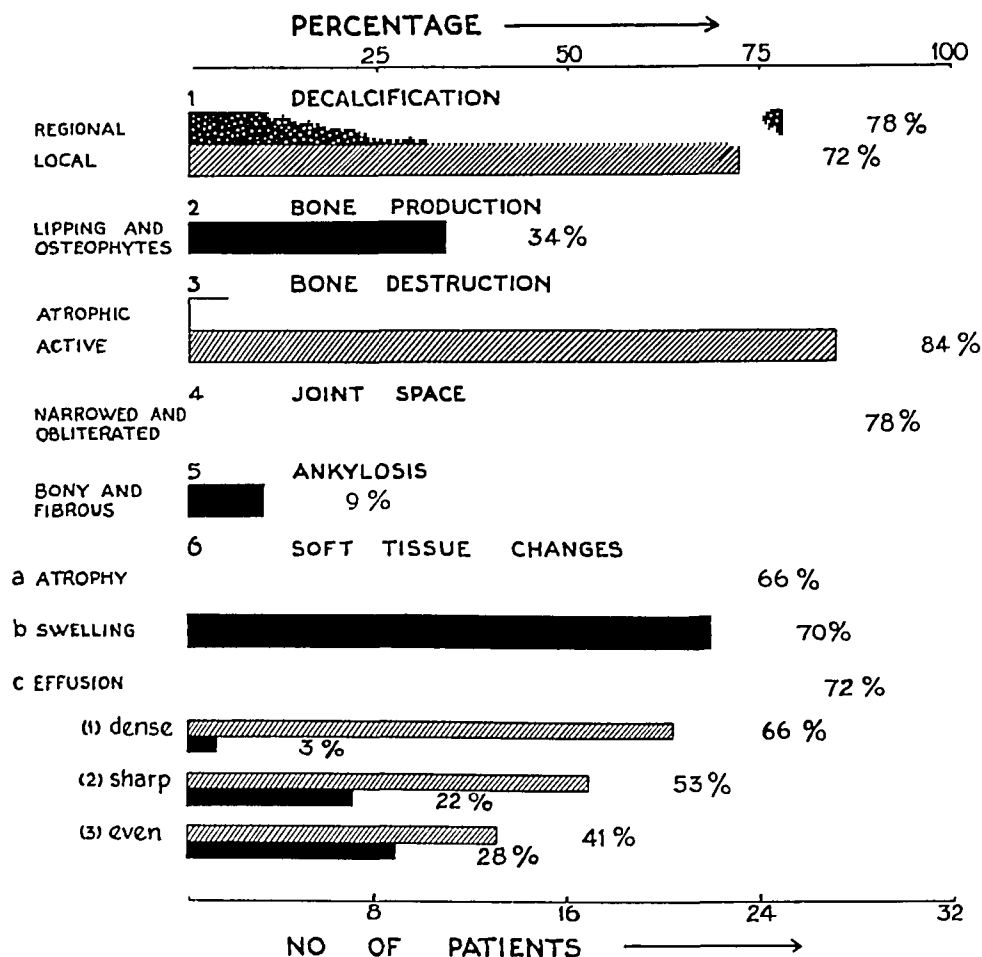


Fig 8—Observations on patients with tuberculous arthritis

Since the present communication is in the nature of a preliminary report, there is little opportunity to discuss the findings of other investigators in the field of tuberculous arthritis. Brief mention should be made, however, of the results of the excellent studies of Allison and Ghormley,<sup>1a</sup> Pomeranz,<sup>7</sup> Phemister and Hatcher,<sup>8</sup> Ghormley, Kirklin and Brav,<sup>9</sup> and Brailsford.<sup>1d</sup> All these authors have pointed out that

<sup>7</sup> Pomeranz, M. M. *Am J Roentgenol* **29** 753, 1933

<sup>8</sup> Phemister, D. B., and Hatcher, C. H. *Am J Roentgenol* **29** 736, 1933

<sup>9</sup> Ghormley, R. K., Kirklin, B. R., and Brav, E. A. *Am J Roentgenol* **30** 747, 1932

the diagnosis of tuberculous arthritis is difficult in the earlier stages of the disease. In cases of moderately well advanced involvement a characteristic picture is usually present. Phemister and Hatcher insisted that the destruction of cartilage occurs late in the course of tuberculous arthritis. In our experience, however, a definite degree of such destruction can usually be demonstrated by the time the patient comes for

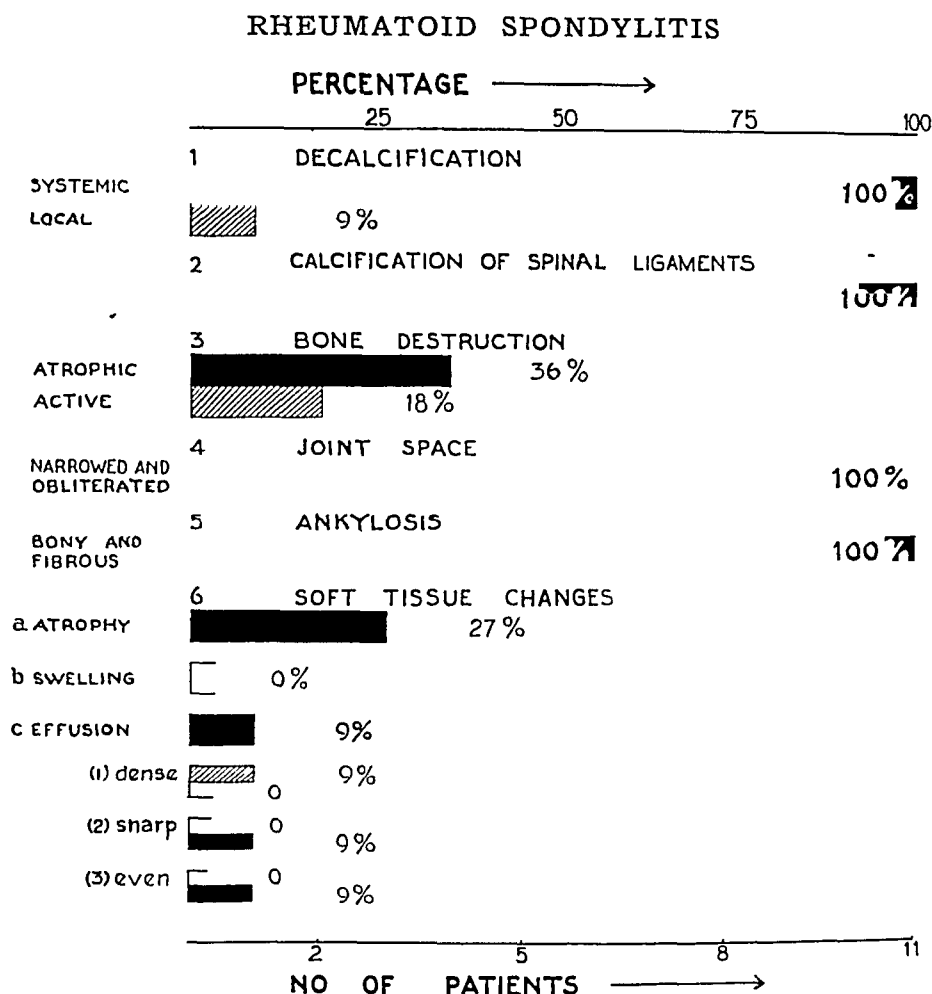


Fig 9—Observations on patients with rheumatoid spondylitis (Marie-Strumpell)

examination. We agree with the statement of Ghormley, Kirklin and Biav that while the destruction of cartilage may be more rapid in other types of arthritis, this form of differentiation is by no means conclusive. It is also pointed out that rapidity of destruction can be determined only by successive examinations and that it is not synonymous with the degree of destruction.

*Rheumatoid Spondylitis (Marie-Strumpell)* (Fig 9, 11 Patients, 33 Joints)—The roentgenologic observations in the cases of rheumatoid spondylitis were similar to those noted in cases of rheumatoid arthritis,

except for the anatomic distribution. The atrophic destruction of bone and the changes in the soft tissues were not well defined because of the location of the affected joints in the spine.

Systemic decalcification was present in 100 per cent of the cases.

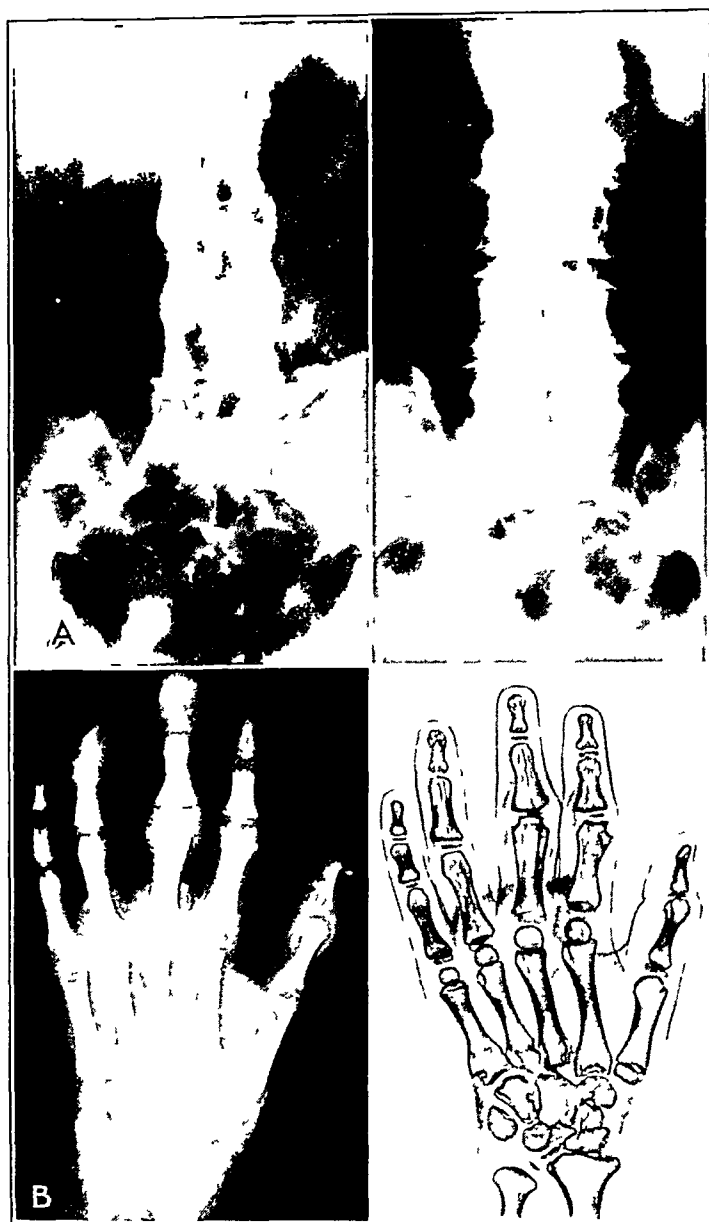


Fig 10—In *A* the roentgenogram at the left is of a patient with rheumatoid spondylitis (Marie-Strumpell), showing systemic decalcification, narrowing and obliteration of the spaces between the facets of the articular processes, calcification of the longitudinal ligaments and obliteration of the sacro-iliac joints. The roentgenogram at the right is of a patient with osteo-arthritis of the spine, showing absence of decalcification, lipping and osteophytes and the sacro-iliac joints relatively well preserved. *B* is a roentgenogram and drawing of a patient with Still's disease, showing systemic decalcification, atrophic destruction of bone, narrowing of the joint spaces, swelling of the soft tissues and effusion, symmetrical and especially well marked about the proximal interphalangeal joints.



## COMMENT

The present study of the roentgen observations on various forms of chronic arthritis has been made on selected groups of cases in which were present only the characteristic clinical and laboratory findings of the type of arthritis they represented. The following changes, observed roentgenologically, have been studied in detail: (1) decalcification, (2) production of bone, (3) destruction of bone, (4) changes in the joint space, (5) ankylosis and (6) shadows made by the soft tissues. No attempt has been made to describe in detail other characteristic roentgen findings or to correlate the type of arthritis with the particular joints involved. It has been noted, however, that for each of the types of chronic arthritis studied there was a basic grouping of pattern of roentgenologic findings.

In submitting these patterns of roentgen findings as being characteristic for the various forms of chronic arthritis, it must be emphasized that the observations and interpretations are based on a much larger series of cases than those actually listed in the figures in this particular report. Regarding exceptional features in these patterns, such as the fact that local decalcification was noted in 13 per cent of the cases of rheumatoid arthritis, it must be understood that several joints were examined in most of the cases and some of these joints may well have been affected by complicating factors, such as previous trauma. In each case, however, there were usually 1 or 2 joints in which the condition conformed completely to the pattern described. The necessity of examining more than one area is emphasized, and it is recommended that the hands, feet, knees and lumbar portion of the spine be examined as routine, regardless of the joints of which the patient complains.

This study has emphasized the importance of many well recognized features to be noted in the roentgen examination of a patient with chronic arthritis, but, in addition, attention is called to certain findings which are less generally appreciated.

One of the prominent features of the roentgen findings in cases of chronic arthritis is the appearance and nature of the shadows made by the soft tissues. These shadows, which are frequently overlooked, are of the utmost importance in the differential diagnosis of the various forms of chronic arthritis. For example, the swelling of the soft tissues in cases of gout is so characteristically eccentric to the joint that it is sometimes possible to make a reasonably certain diagnosis on the basis of this one feature. In order to determine with reasonable accuracy the degree and extent of the changes in the soft tissue, it is necessary to have anteroposterior and lateral views of corresponding joints of the extremities.



It has been more or less generally recognized that atrophic destruction of bone (so-called punched-out areas) constitutes a highly characteristic feature of gout. Our observations have demonstrated that this appearance occurs as frequently in rheumatoid arthritis as it does in gout. It should be mentioned, however, that the size of the areas observed in cases of rheumatoid arthritis is rarely as large as that seen in cases of gout in an advanced stage.

Attention is called to the fact that roentgenograms may show little or no change in the early stages of rheumatoid arthritis, osteo-arthritis, rheumatoid spondylitis (Marie-Strumpell), gout, Still's disease or tuberculous arthritis. In the early stages of gonococcic arthritis, however, the roentgenograms are frequently of the greatest assistance in establishing a diagnosis. In this connection it is again emphasized that the roentgenologist should know at least the duration and severity of the symptoms in the joints in order to make a rational interpretation of the roentgen shadows. The appearance of a joint with gonococcic involvement of six weeks' duration may closely resemble the appearance of a joint with tuberculous involvement of six months' duration.

The results of the study offer considerable evidence in support of the clinical conception that rheumatoid arthritis, Still's disease and rheumatoid spondylitis (Marie-Strumpell) are intimately related. The roentgenologic picture of Still's disease has been found to be identical with that of rheumatoid arthritis in adults, while the picture presented by rheumatoid spondylitis (Marie-Strumpell) differs from that of rheumatoid arthritis only in the anatomic distribution of the articular involvement. It is important to note, moreover, that no evidence has been obtained which would warrant any subdivision of rheumatoid arthritis. In cases in which the atrophic features predominate, essentially the same roentgenologic picture is present as in the cases in which there is more obvious evidence of infection and inflammation. Also, it must be pointed out that rheumatoid arthritis and osteo-arthritis appear to be distinct entities on roentgen examination. Even in cases in which both types occur in the same patient, or even in the same joint, it is usually possible to demonstrate the characteristic changes of each type of arthritis in the roentgen film.

The differentiation between rheumatoid spondylitis (Marie-Strumpell) and osteo-arthritis of the spine has not been specifically referred to in this report. However, it is obvious from what has been said that those two forms of arthritis of the spine are considered to represent merely special forms of rheumatoid arthritis and osteo-arthritis, respectively. The roentgenologic differentiation between these two

varieties of arthritis has recently been insisted on by Miller,<sup>10</sup> Scott<sup>11</sup> and Forestier and Robert<sup>12</sup> and our findings are in agreement with theirs. This phase of the problem will be dealt with in greater detail in a subsequent publication.

Attention is directed to the observation that there appears to be some relationship, as yet unexplained, between gonococcic infection and the arthritic changes observed in (a) the metatarsophalangeal joints, (b) certain types of calcaneal spurs and (c) some types of spondylitis. Also, an occasional puzzling case has been encountered in which the presence of a gonococcic infection has apparently modified the appearance of coexisting rheumatoid arthritis.

In conclusion, it must be emphasized that no single roentgenologic feature is a diagnostic criterion for any one type of chronic arthritis. For example, in any one of the varieties of chronic arthritis there may occur some degree of (1) local decalcification, (2) production of bone, (3) narrowing of the joint space (destruction of cartilage) or (4) ankylosis (in uncomplicated cases of osteo-arthritis, ankylosis occurs only in the spine and in the sacro-iliac joints). Nevertheless, in each group of these cases with clinically typical manifestations a basic pattern or grouping of roentgenologic findings has been observed. It is significant that in the present study of groups with clinically typical changes the roentgenologists' diagnosis was in agreement with the clinical diagnosis in all the cases selected.

Further details will be reported later, dealing with the correlation between the laboratory and the roentgen findings and between the early and the late changes in each type of arthritis. Cases of borderline and doubtful types will be discussed, as well as the appearance of other types of lesions of the joints that may require differentiation from the common types of chronic arthritis.

#### SUMMARY

The roentgenologic findings in representative groups of cases of the following forms of chronic arthritis have been described: (1) rheumatoid arthritis, (2) osteo-arthritis, (3) gout, (4) gonococcic arthritis, (5) tuberculous arthritis, (6) rheumatoid spondylitis (Marie-Strumpell) and (7) Still's disease.

In each of these varieties of chronic arthritis there is a basic pattern or grouping of roentgenologic findings.

10 Miller, J. L. Chronic Rheumatic Diseases of the Spine, *Arch. Int. Med.* **54**: 161 (Aug.) 1934.

11 Scott, S. Gilbert. *Acta rheumatol.* **23**: 7, 1934.

12 Forestier, J., and Robert, P. *Gaz. med. de France (suppl. radiol.)*, May 1, 1934, p. 196.

Rheumatoid arthritis and osteo-arthritis are seen by roentgenogram to be distinct entities

In rheumatoid spondylitis (Marie-Strumpell) and osteo-arthritis of the spine distinct roentgenologic appearances are noted

In rheumatoid arthritis, Still's disease and rheumatoid spondylitis (Marie-Strumpell) the same characteristic grouping of roentgenologic findings is present

Cases of rheumatoid arthritis cannot be divided into subgroups according to observations made on roentgen examination

Atrophic destruction of bone (punched-out area) is observed as frequently in cases of rheumatoid arthritis as in cases of gout

Roentgenograms, properly interpreted, are a valuable aid in the differential diagnosis and prognosis of the various types of chronic arthritis

# MEDULLARY TUMOR OF THE ADRENAL GLANDS

WITH HYPERTENSION AND JUVENILE ARTERIOSCLEROSIS

D N KREMER, M D

PHILADELPHIA

The occurrence of tumors involving the medulla of the adrenal glands is uncommon enough to arouse interest. The finding of such a tumor in each adrenal gland, complicated by hypertension and by marked generalized arteriosclerosis, in a person of 14 years, whose death was immediately due to cerebral thrombosis, merits report.

In a review of the early literature concerning the adrenal glands, there was some confusion, as the early reports were concerned chiefly with the pathologic point of view and neoplasms of these glands were considered rare and of little clinical import. With the increased information on the physiology and pathology of the adrenal glands, there has been greater appreciation of the rôle played by them in causing clinical manifestations of disease.

The factors causing associated hypertension in paraganglioma of the adrenal glands are still not definitely known. However, the recent literature is replete with reports of cases of hypertension and associated clinical manifestations, which have been relieved or cured by surgical intervention and the removal of chromaffin tumors of the adrenal glands and of other growths of the chromaffin system. Pincoffs<sup>1</sup> recently reported three such cases. The main conclusions reached were that the paroxysmal nature of the hypertension may be overlooked because of failure to recognize the early symptoms, which are those of sympatheticonia, and, unless frequent determinations of blood pressure are made at the right time, may be entirely overlooked. The importance of such early clinical determinations is evident in that the tumor may be amenable to surgical intervention, because in almost all cases such a growth is encapsulated and is free from metastasis.

The following case report illustrates the finding of a medullary tumor in each adrenal gland in a young patient, whose condition was diagnosed as hypertensive heart disease with associated glomerular nephritis and whose death was attributed to acute cardiac failure with cerebral catastrophe.

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From the Medical Service, Philadelphia General Hospital

1 Pincoffs, M. Paper read at meeting of American College of Physicians, Philadelphia, April 30, 1935.

## REPORT OF A CASE

N F, a girl aged 14 years, was admitted to the medical service of Dr F J Kalteyer, at the Philadelphia General Hospital, on Nov 17, 1934, the chief complaint was attacks of coughing for the past three weeks

*History*—The birth was normal, the weight was 10 pounds (4,535 Gm), and there was no trauma at delivery. She was breast fed until the age of 18 months, and development was normal. Teething began at 10 months, and she walked at 12 months. She had diphtheria at 4 years and scarlet fever at 5 years, with ten weeks' convalescence at the Philadelphia Hospital for Contagious Diseases. At that time and immediately afterward there was no history or any evidence of acute nephritis. She had pertussis at the age of 5½ years. Tonsillectomy was done at 6 years. She was admitted in March 1928, at the age of 8 years, to the Graduate Hospital of the University of Pennsylvania with a history of shortness of breath and cough. She remained two weeks and was readmitted in November 1929 to the same hospital with the same complaints. During these periods of hospitalization, repeated examinations of the urine showed a variable specific gravity, from 1.010 to 1.025, the reaction to tests for albumin varied from negative to plus two, and there was an occasional hyaline cast. The blood pressure (one reading on each admission) was 90 and 95 systolic and 60 diastolic. The urea nitrogen content of the blood on Nov 15, 1929, was 15 mg per hundred cubic centimeters of whole blood. When phenolsulfonphthalein was administered on the same day, 50 per cent was excreted in one hour and 25 per cent in two hours. The basal metabolic rate on November 25 was +34. She was discharged with the diagnosis of parenchymatous nephritis. She was readmitted to another hospital in March 1931, with a history of cardiac pain and palpitation. At that time, examination of the urine showed hyaline and granular casts. The whole blood contained 15 mg of urea nitrogen, 11.6 mg of calcium and 125 mg of sugar per hundred cubic centimeters. The serum contained 8.9 per cent protein, 6.3 per cent albumin and 2.6 per cent globulin. The results of repeated serologic examinations were negative. She was readmitted to the same hospital on June 15, 1932, in a stupor, with facial and peripheral edema. The blood pressure was 130 systolic and 110 diastolic. On the recovery of the patient from coma the blood pressure was 185 systolic and 140 diastolic. Studies of the eyegrounds were made at that time, and the report was nephritic retinitis, with arteriosclerosis incident to hypertension. There was bilateral atrophy of the optic nerve. Analysis of the blood showed 14 mg of urea nitrogen per hundred cubic centimeters, 3.5 mg of uric acid and 1.4 mg of creatinine.

The third admission was on Oct 31, 1933. The blood pressure was 172 systolic and 110 diastolic. Examination of the eyegrounds revealed old and new retinal hemorrhages, and examination of the visual fields revealed reduction to central vision. Examination of the urine revealed a specific gravity of 1.028. The blood contained 15.2 mg of urea nitrogen per hundred cubic centimeters.

At the time of the fourth admission the blood pressure was 206 systolic and 152 diastolic. The heart was markedly enlarged. A roentgenogram of the skull showed that the sella turcica was normal. The diagnosis was chronic diffuse nephritis with hypertension.

When the patient was admitted to our service, the main symptom was attacks of severe coughing, which was aggravated by exertion, worse at night and non-productive, without hemoptysis.

*General Examination*—The patient weighed 85 pounds (38 Kg). She was stubborn and somewhat spoiled. Her stature was shorter than normal. There

was some kyphosis of the thoracic portion of the spine. The pelvis was well developed and was of the same width as the shoulders. The hands and feet were small. There was marked genu valgum on each side.

The outstanding abnormality of the skin was a mottled, dusky red, spider-web pigmentation of the lower part of the arms and legs and a coarser texture than normal (keratosis pilaris).

The body was somewhat full in the trunk, and the abdomen was prominent. The breasts were small and were not well developed for the patient's age and race.

The upper and lower extremities were normal. There was a growth of fine hair over the forehead and the body. The pelvic hair line was normal. On the arms and legs there was a universal distribution of hair, which was short, coarse and poorly pigmented.

The pupil of the right eye was larger than that of the left. There was no nystagmus. In the right eye the media were clear and the disk was well defined and almost white. The physiologic cup was filled, the veins were normal, and the arteries were small and sclerosed, some being represented mostly by a white line. The fundus throughout showed considerable degeneration, with numerous small atrophic areas and exudates. The condition of the left eye was the same. The diagnosis was atrophy of the optic nerve and retina, probably secondary to neuroretinitis.

There was hypertrichosis. The face appeared old, the fingers were tapered, and the hands were small and stubby. The thyroid gland was slightly enlarged.

Occasional fine râles were heard at the bases of the lungs, which were otherwise normal.

The blood pressure was 190 systolic and 150 diastolic. The cardiac impulse was rapid, regular, powerful and diffuse. The apex beat was heard at the fifth interspace 8 cm. from the midsternal line. There were no murmurs. The aortic second sound was greater than the pulmonic second sound and was accentuated. The pulses were equal, regular and of good volume.

The liver and spleen were not palpable.

Roentgenograms made on November 18 showed that the transverse diameter of the heart was enlarged to approximately 13 cm. and that the transverse diameter of the chest was 21 cm. The supracardiac shadow was slightly widened. In a roentgenogram taken in the right oblique position the retrocardiac space was shown to be obliterated and the barium sulfate-filled esophagus was shown to be displaced backward. There was considerable haziness over both pulmonary fields. The cardiac silhouette was suggestive of a bilateral mitral lesion. There was passive congestion of the lungs.

An orthodiagram was made on November 19. The total intrathoracic diameter was 22.6 cm., and the total cardiac diameter, 13 cm. The heart was considerably enlarged, having a rounded, prominent left ventricle. These features were salient characteristics of considerable hypertrophy.

An electrocardiogram taken on November 19 showed some left axis deviation. The T wave was inverted in leads 1 and 2. This indicated the severe strain that the heart was under as a result of the hypertension.

On November 18 a roentgenogram showed that the bones of the skull were normal. There was no evidence of convolitional atrophy. The clinoid processes appeared slightly enlarged, and the posterior processes were somewhat bulging.

*Laboratory Examination*—The specific gravity of the urine was from 1.016 to 1.029. The reaction to tests for albumin was from + to ++. There was no sugar. The urine contained an occasional granular cast but no red blood cells.

On Nov 21, 1934, when the phenolsulfonphthalein test was made, 10 per cent was excreted in the first hour and 20 per cent in the second hour—a total of 35 per cent

Chemical analysis of the blood serum showed 3.64 Gm of albumin per hundred cubic centimeters, 2.62 Gm of globulin and 6.26 Gm of total protein. On November 19 the red cell count was 5,100,000 and the white cell count was 17,050



Fig 1—Gross specimen of adrenal glands

On November 21 the red cell count was 5,540,000 and the white cell count was 17,700. Chemical analysis of the blood showed 102 mg of sugar per hundred cubic centimeters, 9 mg of urea nitrogen and 548 mg of chlorides.

*Course*—On December 1 there were stupor and breathing of the Cheyne-Stokes type. The reflexes were increased, there was marked ankle clonus, and the Babinski sign was not present. There was pulmonary edema. The patient died suddenly at 5 a. m.

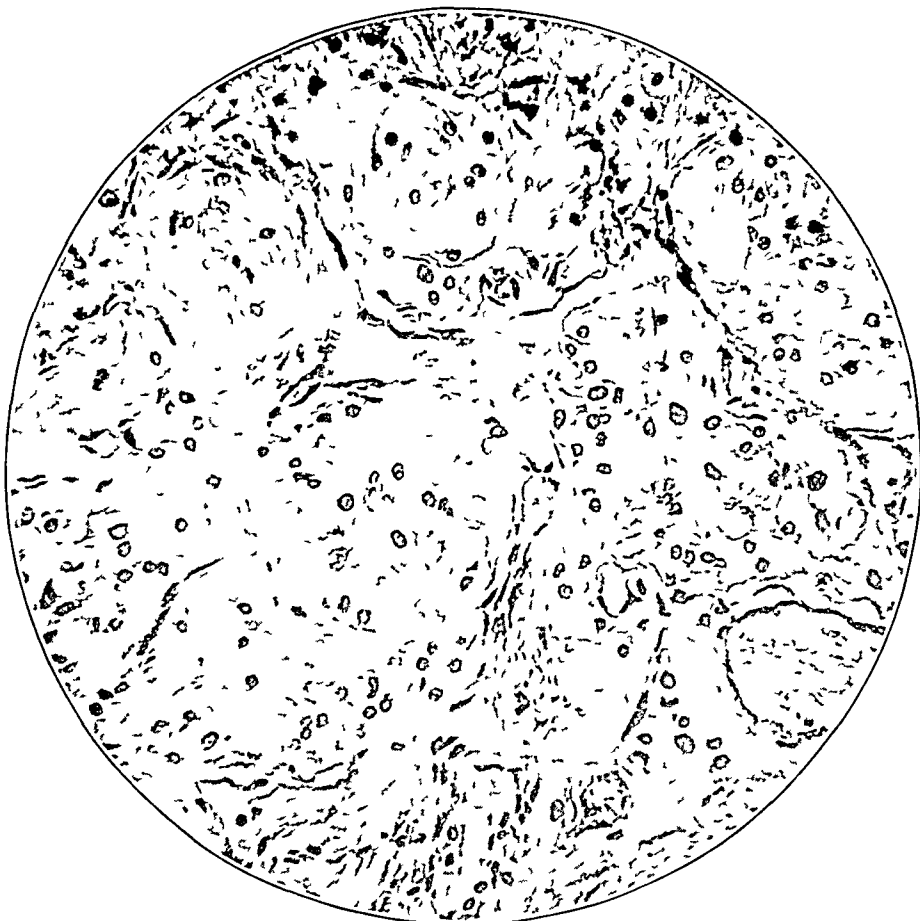


Fig 2—A section from the adrenal tumor, showing a typical alveolar arrangement of the cells bearing chromaffin granules with septums formed by delicate wavy spindle cells with long fibrillar cytoplasmic terminals ( $\times 149$ )

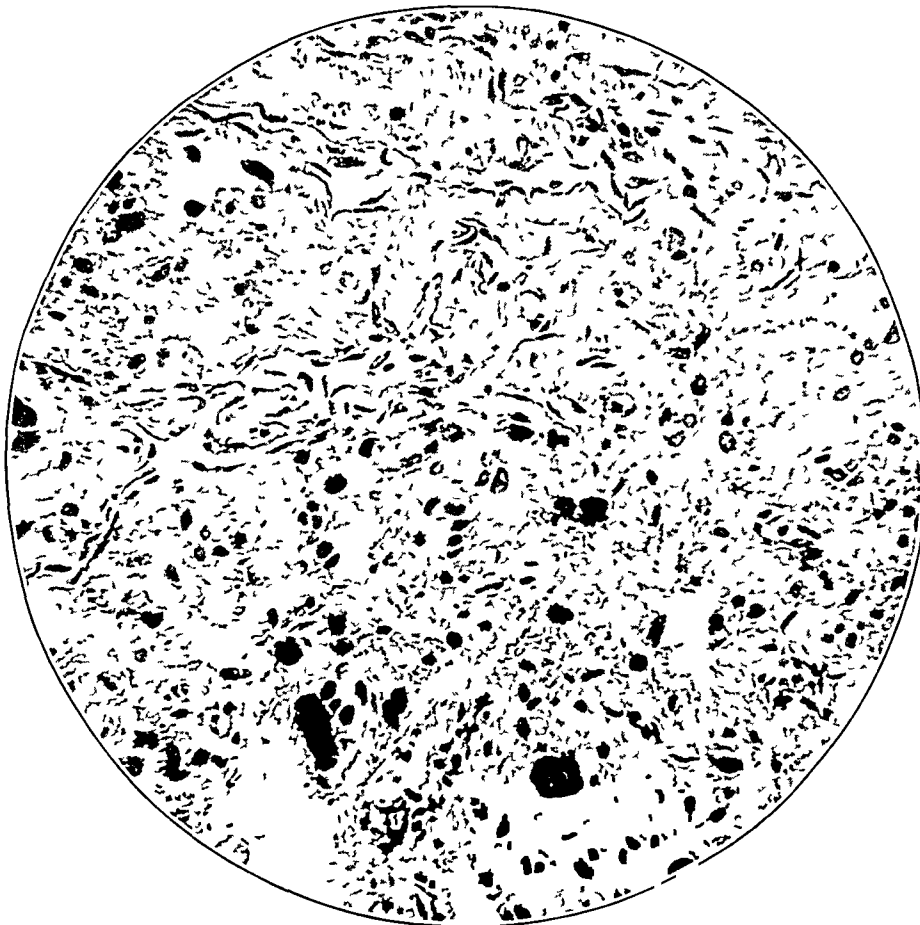


Fig 3—A section from the adrenal tumor, showing variation of cell type with the appearance of an occasional giant form, ( $\times 149$ )



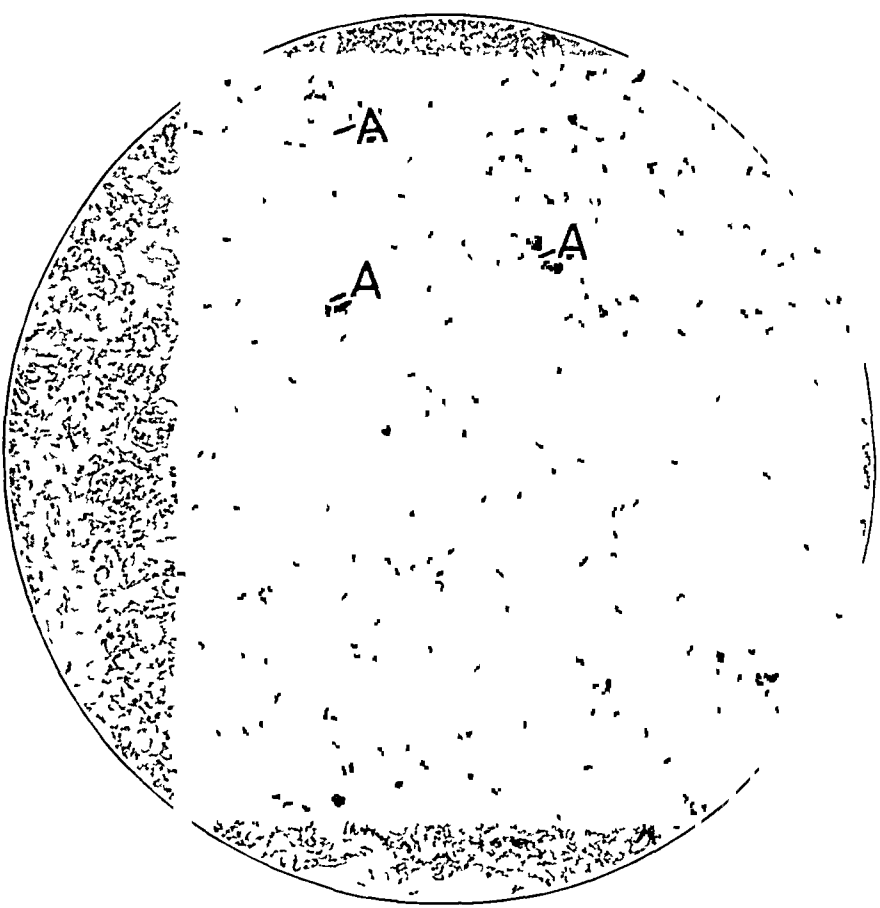


Fig 4—A section from the kidney under low power magnification ( $\times 38$ ), showing thrombotic lesions of the arterioles and tufts at the points marked *A*



Fig 5—Photomicrograph of a section from the kidney, showing intraglomerular thromboses of one tuft at *A*, arteriolar proliferation at *B*, hyalinization of convoluted tubular epithelium at *C* and interstitial round cell infiltration at *D* ( $\times 149$ )

*Autopsy*—Macroscopic Anatomic Examination There was mild obesity The skin showed keratosis pilaris The breasts were underdeveloped The aorta showed juvenile atherosclerosis The heart showed marked concentric myocardial hypertrophy of the hypertensive type, and degeneration was present There was acute passive congestion of the lungs, with edema and multiple hemorrhagic infarcts There were acute and chronic passive congestion of the spleen, acute passive congestion of the kidneys and passive congestion of the bladder The uterus was juvenile, and there were simple cystomas of the ovaries Passive congestion was present in the gastro-intestinal tract The liver showed mild parenchymal degeneration and acute passive congestion The gallbladder was apparently normal There was passive congestion of the pancreas The adrenal glands showed bilateral neuroma ganglionare The skeleton was apparently normal Hyperplasia was present in the perirenal lymph nodes on the left side There were thrombosis of the blood vessels of the left hemisphere of the cerebrum, internal hydrocephalus and atrophy of the optic chiasm

The kidneys weighed 150 Gm each The capsules were thin and stripped with ease, leaving a firm, dark red, smooth surface, but beneath the left adrenal gland the parenchyma had a lighter, reddish-brown hue On sectioning, the cut edges were sharp, and blood oozed from the cut surface The corticomedullary ratio was normal The pelves and ureters were normal

The left adrenal gland weighed 70 Gm, the right, 35 Gm Both were greatly enlarged, the right was fairly uniform, but the left was slightly nodular There was a slight enlargement of the adjacent lymph nodes on the left, they were firm and had a homogeneous, grayish appearance On sectioning, the two adrenal glands showed a similar appearance The cortex was thin and yellowish brown, encircling the tumor but not apparently being involved The tumor was irregularly yellowish brown and reddish gray, with a few grayish fibrous trabeculae, most of the medulla was replaced by tumor tissue, that which remained was firm and dark red

*Histologic Examination* There were moderate atherosclerosis of the aorta, marked myocardial hypertrophy and degeneration, and marked sclerosis of the coronary vessels The lungs showed hemorrhagic infarction, recent venous thrombosis, arteriosclerosis and acute and chronic passive congestion There was acute and chronic passive congestion of the spleen, as well as arteriosclerosis In the kidneys there were recent anemic infarcts, arteriolar and intraglomerular hyaline thrombosis, severe tubular hyalinization and mild eccentric thickening of the intima of the renal arteries Hypoplasia and arteriolar hyalinization were present in the uterus The ovaries showed follicular cystomas, arteriosclerosis and acute passive congestion There was moderate parenchymal degeneration of the liver, with leukocytic stasis and mild fat infiltration The pancreas showed mild parenchymal degeneration and marked arteriosclerosis Pronounced arteriosclerosis was also present in the thyroid gland and in the diaphragm There was a paraganglioma in each adrenal gland

*Pathologic Diagnosis* Death was caused by hypertensive heart disease, thrombosis of the vessels of the left hemisphere of the cerebrum and paraganglioma

#### COMMENT

The presence of hypertension in a young person who was found to have a medullary tumor of each adrenal gland raises the question of what part, if any, the paragangliomas had in the causation of the hyper-

tension The theory that hypertension is the result of an increase in the amount of circulating epinephrine is questionable Nevertheless, Elliot and Nuzum<sup>2</sup> expressed the belief, as a result of their studies, that there is the possibility of a pressor principle in the circulating blood in persons with arterial hypertension It is possible that overactivity of the chromaffin system is internally related to sclerosis of the finer arterioles, such as takes place in contracted kidneys, but has no bearing in the causation of atherosclerosis of the larger vessels Tumors involving the chromaffin cells of the adrenal glands are accompanied by crises of hypertension, which may be very severe These tumors seem to act by an excessive gradual or sudden discharge of epinephrine into the blood stream This causes a dysfunction of the regulatory mechanism for arterial tension, thus resulting in an intense vasoconstriction and a subsequent rise in blood pressure Konschegg<sup>3</sup> claimed that he was able to determine an increase in the amount of a lipid substance combined with epinephrine in the blood of patients with hypertension Frei<sup>4</sup> concluded that when hypertension occurs in the young, with the presence of associated organic changes, such as arteriosclerosis, disease of the kidneys and cardiac hypertrophy, one should consider the possibility of changes in the adrenal glands Laubry and Bernal,<sup>5</sup> in their discussion of a case of medullary tumor of the adrenal glands, arrived at the following conclusions The clinical history may be divided into two distinct phases In the first, the crises of paroxysmal hypertension are separated by intervals in which the pressure is normal and in which the functional disturbances which accompany the sudden differences of pressure level are absent In the second, the crises of pressure increase and occur with greater frequency, the hypertension becoming permanent, and at the same time there is a manifestation of renal lesions and subsequent organic changes depending on the permanent hypertension

#### SUMMARY

In a patient with juvenile hypertension, who died of cerebral thrombosis, postmortem examination revealed paraganglioma of each adrenal gland The following conclusions are tenable 1 Careful consideration of the clinical history precludes the possibility of primary hemor-

2 Elliot, Albert H, and Nuzum, Franklin R J Lab & Clin Med **18** 1255 (Sept) 1933

3 Konschegg, T Mechanism of Normal and Increased Blood Pressure, Klin Wchnschr **13** 1452 (Oct 13) 1934

4 Frei, Walter Nebennierenmark und Hypertonie, Frankfurt Ztschr f Path **46** 523, 1934

5 Laubry, Charles, and Bernal, P Paraganglioma of Medulla, Bull et mem Soc med d hôp de Paris **50** 658, 1934

rhagic nephritis which had passed into a chronic phase with associated organic changes. The early and late absence of dysfunction of the kidneys, the normal range of specific gravity of the urine and the normal blood are in favor of this view. 2 The evidence of glandular dysfunction as evinced by the character of the distribution of the hair and fat and the lack of full sex development for the patient's age and race suggest some pituitary factor indirectly influenced by the adrenal hormones. 3 Early in the history, the symptoms causing hospitalization, such as precordial pain, cardiac palpitation and dyspnea, were suggestive of hypertensive crises, although in two studies readings of blood pressure were normal. 4 Later findings of persistent hypertonia, changes in the eyegrounds and cardiac hypertrophy were indicative of permanent organic changes.

On the basis of these conclusions, one is justified in considering this a case of hypertension due to an adrenal factor, with early symptoms of a paroxysmal type of vascular crisis, which was not recognized. Later, a fixed hypertension merged into the malignant state, with all the organic changes concomitant in such a condition. The occurrence of hypertension in the young, with failure to discover the cause for such a condition, should always suggest the possibility of chromaffin tumor of the adrenal glands.

# DISTURBANCE OF ACTION OF RESPIRATORY MUSCLES AS A CONTRIBUTING CAUSE OF DYSPNEA

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It has long been recognized that the existence and severity of dyspnea in persons with diseases of the heart and lungs often bear little relation to disturbances in the acid-base equilibrium or in the aeration of the blood. This was suggested by the work of Krogh and Lindhard<sup>1</sup> on muscular exercise as long ago as 1913 and was definitely described by Peabody and Wentworth<sup>2</sup> in 1917 in certain cases of cardiac disease with dyspnea. Further evidence to the same effect has more recently been brought forward by Anthony,<sup>3</sup> Cullen and his associates,<sup>4</sup> Knipping, Lewis and Moncrieff<sup>5</sup> and others.

The importance of the mechanics of breathing in the causation of dyspnea has received adequate attention only in recent years, owing perhaps in part to the great advances made, especially between 1914 and 1928, in the knowledge of the acid-base equilibrium of the body and particularly of the physical chemistry of the blood, with correspondingly less attention given to other phases of the subject. Probably the contribution that did more than any other to restore a proper con-

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1 Krogh, A, and Lindhard, J. Regulation of Respiration and Circulation during the Initial Stages of Muscular Work, *J Physiol* **47** 112, 1913.

2 Peabody, F W, and Wentworth, J A. Clinical Studies of the Respiration. IV The Vital Capacity of the Lungs and Its Relation to Dyspnea, *Arch Int Med* **20** 443 (Sept) 1917.

3 Anthony, A J. Zur Frage der Stenosenatmung, *Beitr z Klin d Tuberk* **70** 452, 1928.

4 Cullen, G E, Harrison, T R, Calhoun, J A, Wilkins, W E, and Tims, M M. Relation of Dyspnea of Exertion to the Oxygen Saturation and Acid-Base Condition of the Blood, *J Clin Investigation* **10** 807, 1931.

5 Knipping, H W, Lewis, W, and Moncrieff, A. Ueber die Dyspnoe, *Beitr z Klin d Tuberk* **79** 1, 1931.

ception of the balance between the chemical, or humoral, and the physical, or mechanical, phases of breathing was that of Hess<sup>6</sup> in 1931. This dealt almost wholly with physiologic and pharmacologic rather than with clinical material. Both from earlier work of others and from his own observations, Hess developed the theory that chemical (humoral) stimuli derived from tissue metabolism determine the volume of breathing and physical stimuli, or those derived from the air passages and the moving framework of the chest, determine its form.

Considered in the whole category of mechanical movements producing pulmonary ventilation, the activities of nearly all the muscles of the thorax and abdomen and secondarily those of the extremities also are concerned in the maintenance of the equilibrium within which the act of breathing proceeds. Among the dynamic types of equilibrium are those which maintain pressure relations in the chest and abdomen, with the diaphragm serving in part as a single partition between these (Schoen and Hempel<sup>7</sup>). Roentgen kymographic study (Dahm,<sup>8</sup> Cramer, Wilke and Weber<sup>9</sup>) has further shown dynamic relationships between various groups of respiratory muscles and their bony attachments during different phases of breathing. These authors (and Felix<sup>10</sup>) conclusively demonstrated the existence of synergy and antagonism of movement of these groups of muscles.

A description of the whole integrated mechanism of breathing from the point of view of its nervous regulation has been written recently by Fleisch<sup>11</sup>. Following Hess, Fleisch conceived of the central regulating mechanism ("respiratory center") as imposing a definite ventilatory exchange of air, with respiratory and expiratory phases. The proprioceptive impulses, streaming into the respiratory center from all parts of the breathing mechanism, determine the manner and the intensity of the act of breathing, whereby the required ventilation is accomplished.

The relation of the phenomenon of subjective dyspnea to abnormalities or defects in the mechanics of the respiratory or circulatory system has been developed by several recent workers (Harrison and

6 Hess, W. R. *Die Regulierung der Atmung, gleichzeitig ein Beitrag zur Physiologie des vegetativen Nervensystems*, Leipzig, Georg Thieme, 1931.

7 Schoen, R., and Hempel, J. Ueber schlaffe und gespannte Apnoe, *Arch f exper Path u Pharmacol* **171** 403, 1933.

8 Dahm, Max. Rippen- und Zwerchfellbewegung im Rontgenbild, *Fortschr a d geb d Rontgenstrahlen* **47** 276, 1933.

9 Cramer, H., Wilke, A., and Weber, H. H. Zur Rontgenkymographie der Thoraxorgane, *Klin Wchnschr* **12** 179, 1933.

10 Felix, W., in Sauerbruch, E. F. *Die Chirurgie der Brustorgane*, ed. 3, Berlin, Julius Springer, 1928.

11 Fleisch, A. Neuere Ergebnisse uiber Mechanik und proprioceptive Steuerung der Atmungsbewegung, *Ergebn d Physiol* **36** 249, 1934.

his associates,<sup>12</sup> Knipping,<sup>13</sup> Herbst,<sup>14</sup> Storm van Leeuwen, van Niekerk and Weltz,<sup>15</sup> Gavazzoni and Cotti<sup>16</sup>)

The present investigation provides further data on this problem. In brief, we have attempted to study pulmonary and circulatory functions in a patient with pulmonary fibrosis who showed an extreme degree of physical disability due to exertional dyspnea, with almost negligible abnormalities in the aeration of his blood by the lungs and no demonstrable defects in the transport of gases by the circulation.

This case is one of the general group studied especially by Anthony,<sup>3</sup> by Storm van Leeuwen and his associates<sup>15</sup> and by Knipping and his co-workers,<sup>5</sup> in which marked mechanical difficulties of breathing apparently constitute the cause of dyspnea. We have endeavored to analyze the particular mechanical difficulties of breathing suffered by this patient. For purposes of comparison we studied at the same time a second patient with pulmonary fibrosis, who had considerable cyanosis and oxygen unsaturation and a definitely disturbed acid-base equilibrium, yet relatively slight exertional dyspnea, and for further comparison we made a number of measurements on a normal person under the same conditions of rest and exercise as the two patients with pulmonary fibrosis.

CASE 1—J. M. was a salesman, aged 45, suffering from pulmonary fibrosis with dyspnea. The onset of pulmonary tuberculosis with hemoptysis occurred in 1911, and he was treated for eighteen months. From 1913 to 1930 he enjoyed good health. In February 1930 he had a small hemoptysis. He was seen first at the Bellevue Hospital at that time, the diagnosis was healed tuberculosis of the upper lobe of the right lung with productive lesions at the apex of the left lung. The sputum was normal. The heart was apparently normal. The pupils were very small, reacting slightly to light. The Wassermann reactions of the blood and spinal fluid were negative. He was readmitted in July 1931, because of slight hemoptysis. His condition was similar to that noted at the time of the first admission. He was readmitted in May 1932 and again in July 1933, on account of dyspnea on exertion, which had been noticed since early in 1932, appearing after walking or other mild exertion. There was polypnea at rest, without discomfort. There was no dyspnea except on exertion and no cyanosis.

*Examination*—The temperature was normal, the pulse rate from 70 to 80 and the respiratory rate from 30 to 36. The weight was 125 pounds (56.7 Kg). He

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12 Harrison T. R., Harrison, W. G., Jr., Calhoun, J. A., and Marsh, J. P. Congestive Heart Failure. XVII. Mechanism of Dyspnea on Exertion, *Arch Int Med* **50** 690 (Nov.) 1932.

13 Knipping, H. W. Dyspnoe, *Beitr z Klin d Tuberk* **82** 133, 1933.

14 Herbst, R. Die anatomischen und pathologisch-physiologischen Grundlagen des Asthma bronchiale, Immunität Allergie u. Infektionskr. **4** 3, 1933.

15 Storm van Leeuwen, W., van Niekerk, J., and Weltz, G. A. Studien über Atmung und Thoraxform bei Asthma und Emphysem, *München med Wchnschr* **80** 681, 1933.

16 Gavazzoni, M., and Cotti, L. Der Einfluss der Stenosenatmung auf die Lungenventilation bei schwerer Arbeit, *Beitr z Klin d Tuberk* **84** 433, 1934.

was of medium stature, not abnormally slender, with a ptotic posture and flabby muscles. There was no cough or sputum. Examination of the chest revealed a fibrotic type of tuberculosis of the upper lobe and the apex of the right lung, with diminished breath sounds and a normal percussion note. There were no rhonchi or wheezing. The heart was of normal size, and there was a snapping second pulmonic sound. The blood pressure was 120 systolic and 70 diastolic. The other organs were normal. An electrocardiogram showed a slightly low voltage. During his first six weeks in the hospital the patient was extremely dyspneic on slight exertion. In the ensuing nine months there was a gradual increase in tolerance of exercise, with no treatment other than the training involved in many exercise and respiration experiments.

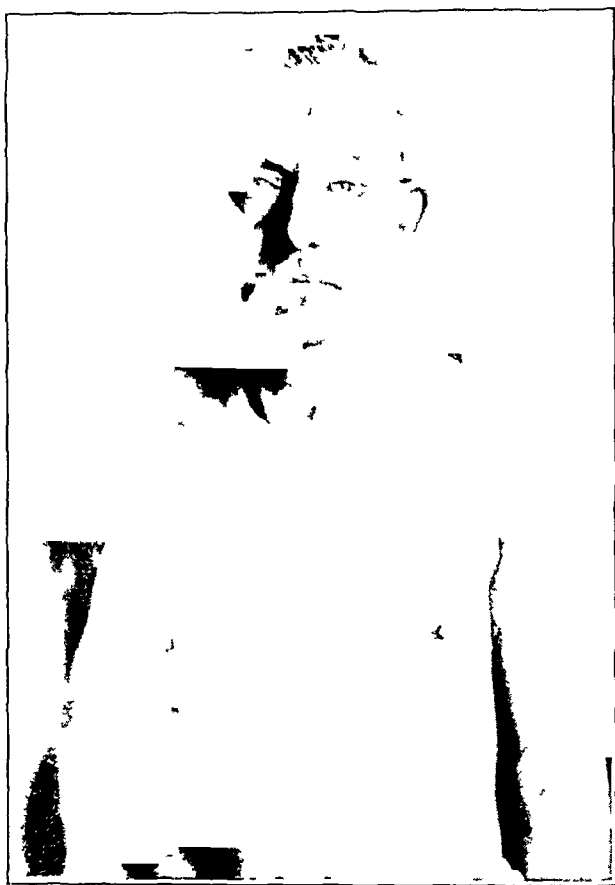


Fig 1—Dyspneic subject during quiet expiration, showing persisting spasm of upper accessory muscles of respiration

CASE 2—A C was a clerk, aged 26, who had advanced chronic pulmonary tuberculosis, with arterial anoxemia, without dyspnea. The onset of tuberculosis occurred in 1927. He was treated for twenty months and was discharged with the condition thought to be arrested. Sudden hemoptysis occurred late in 1932, requiring artificial pneumothorax. There had been loss of weight since then. He was admitted to the Bellevue Hospital in July 1933. He weighed 111 pounds (50.34 Kg) and appeared chronically ill. There was slight cyanosis. Partial pneumothorax was present on the left, limited by pleural adhesions. Cavitation was present in the upper lobe of the left lung. There was slight hyperpnea at rest but no subjective dyspnea. Moderate exertion (stair climbing) could be carried out without dyspnea.



CASE 3—H B was a physician, aged 27, normal but not in good physical training. He weighed 141 pounds (65 Kg) and was 5 feet, 9 inches (175 cm) tall.

#### PROCEDURE

Measurements in the resting state were made both with the subject lying supine and when he was standing.

The form of exercise was simple stepping up and down at a constant rate, using a single step 20 cm high. Two rates, or degrees of exercise, were used, each based on the tolerance of the dyspneic subject for exercise. The first ("fast exercise"), of about thirty-five steps a minute, constituted the maximum exertion which the patient could tolerate for one minute. As a matter of fact, during the early experimental procedures, which were carried out shortly after the patient's admission to the hospital, his tolerance was only twenty or twenty-five steps a minute. Later it improved.

The second ("slow exercise"), of about twenty steps a minute, was an exertion which the dyspneic patient could carry on for several minutes without more than moderate respiratory distress.

The anoxemic patient had slight subjective dyspnea after one minute of the "fast exercise" and none after several minutes of "slow exercise." The normal subject was not dyspneic after either.

For most of the experiments on the blood before and during exercise and for all the experiments on respiration before and during exercise all subjects were under fasting, basal conditions. For most of the experiments on volume of the lungs, roentgen studies and determinations of venous pressure, velocity of flow and volume of blood they had been in the resting state for an hour or more but were not under basal conditions.

#### METHODS

The vital capacity and its subdivisions were recorded graphically, with a standard Benedict-Roth metabolism apparatus, but with a more rapidly moving recording drum. There was an error in the measurements of tidal air and of reserve air performed in this way, owing to the absorption of carbon dioxide during expiration, but this error was small and the necessary correction could be approximated.

Residual air was measured by the method of Christie<sup>17</sup>

For the investigation of pulmonary function, two sets of exercise experiments were performed, one for the purpose of recording graphically the amplitude, frequency and form of respiratory movements and the other for the quantitative measurement of ventilation and total exchange of gases. In both cases, the subject's procedure was essentially the same. He was under fasting, basal conditions. He first stood at rest with the mouthpiece and nose clip attached for five or ten minutes, in order to reach an approximately steady state. The control observations were then made, over a period of one or two minutes. After that, at a signal, exercise was begun, the number of seconds taken for each step being regulated by a stop-watch. Continuous records of respiration were taken from the moment when the signal for beginning exercise was given. After exercise stopped further observations were made during the first two minutes of recovery, while the subject stood still in the same position as during the control period.

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<sup>17</sup> Christie, R V. The Lung Volume and Its Subdivisions. I. Methods of Measurement, *J Clin Investigation* **11** 1099, 1932.

The observations on respiratory movements were recorded graphically, the closed system of a large (9 liter spirometer) Benedict-Roth metabolism apparatus being used and the movements of the spirometer being recorded on a Harvard kymograph moving at a suitable velocity. By means of a three way valve the subject's respiration could be shunted from outside air into the closed system of the apparatus at any desired moment. Continuous records were made over one minute periods. Enough oxygen was introduced into the spirometer beforehand and at one minute intervals during the experiment so that the average concentration of air breathed during the minute was approximately atmospheric.

For the measurement of exchange of gases, the outflow tube from the mouth-piece was connected with a three way valve, which could throw the expired air either into a 120 liter Tissot spirometer or into a Douglas bag. By the alternate use of these containers, several successive volumes of air expired during one minute periods could be obtained and samples removed for analysis. Analyses of the gases were made by the Haldane apparatus.

Samples of arterial blood were drawn and analyzed according to a technic recently described<sup>18</sup>

TABLE 1—*Volume of Lungs During Rest*

Subject	Position	Residual Air, Cc	Reerve Air, Cc	Tidal Air, Cc	Comple- mental Air, Cc	Vital Capacity, Liters	Total Capacity, Liters
J M (dyspneic)	Supine Standing	1,551	689 870	434 504	1,305 839	2.42 2.21	3.97
A C (anoxemic)	Supine Standing	1,673	589 853	706 671	863 343	2.16 1.87	3.83
H B (normal)	Supine	1,116	2,100	722	2,402	5.02	6.13

Venous pressure was measured by the direct method. Intrapleural pressure (anteriorly) was measured on one occasion simultaneously with a determination of venous pressure. The subject was semirecumbent. The velocity of blood flow was determined by intravenous injection of decholin sodium (sodium dehydrocholate), the "velocity" being the number of seconds from the moment of injection to the first sensation of bitter taste in the mouth. The volume of blood was estimated by the dye method, brilliant vital red being used.

Attempts were made with the dyspneic subject to measure the cardiac output during resting, by the use of a method recently described<sup>18</sup>. These attempts were unsuccessful, as the subject did not retain a steady state, so far as respiratory gases were concerned, long enough to permit a determination of cardiac output to be completed.

## RESULTS

From a large amount of data accumulated over seven months' time, typical examples illustrating the behavior of the dyspneic subject, with similar measurements, for comparison, on the other two subjects, are presented in the accompanying tables and figures.

Table 1 gives for each subject average figures for the subdivisions of lung volume, taken with the patient at rest. Further observations,

<sup>18</sup> Richards, D. W., Jr., Cournand, A., and Bryan, N. A. Applicability of Rebreathing Method for Determining Mixed Venous CO<sub>2</sub> in Cases of Chronic Pulmonary Disease. *J. Clin. Investigation* **14**: 173 (March) 1935.

not included in the tables, were made on the dyspneic subject's vital capacity during the period of recovery, from thirty seconds to ten minutes after exercise. There was found to be a definite increase of from

TABLE 2—*Measurements of the Chest of the Dyspneic Subject During Rest, During Deep Inspiration and During Complete Expiration*

	Resting Position	Deep Inspiration	Complete Expiration
Anteroposterior diameter, angle of Louis to sixth dorsal vertebra	18 0	18 5	17 0
Xyphoid process to tenth dorsal vertebra	19 7	21 0	18 5
Lateral diameter, axilla to axilla	27 6	27 8	27 0
Circumference of chest at the level of the ninth dorsal vertebra below pectoralis major	83 0	84 5	81 0

TABLE 3—*Respiratory Functions During Rest and During and After One Minute of Fast Exercise*

	Rest, Standing	Exercise, 1 Minute, 25 Steps	Recovery	
			First Min	Second Min
A—T M (dyspneic)—8/25				
Respiratory rate	27	20	30	28
Pulse rate	87		90	90
Tidal air, cc	370	457	578	505
Ventilation, liters per minute	10 0	9 1	17 4	14 1
Carbon dioxide output, percentage	2 26	2 52	2 63	2 31
Carbon dioxide output, cc per minute	226	230	456	326
Oxygen intake, percentage	2 76	4 19	2 81	2 00
Oxygen intake, cc per minute	276	383	488	283
Respiratory quotient	0 82	0 60	0 93	1 15
1 Minute, 37 Steps				
B—J M (dyspneic)—9/22				
Respiratory rate	36	22	35	36
Pulse rate				
Tidal air, cc	372	550	790	568
Ventilation, liters per minute	13 1	12 1	27 6	20 5
Carbon dioxide output, percentage	1 89	2 55	3 06	2 61
Carbon dioxide output, cc per minute	253	308	902	534
Oxygen intake, percentage	2 20	4 71	3 97	2 60
Oxygen intake, cc per minute	295	570	1,095	531
Respiratory quotient	0 86	0 54	0 82	1 01
1 Minute, 34 Steps				
C—A C (anovemic)—10/26				
Respiratory rate	19	32	43	40
Tidal air, cc	470	490	720	670
Ventilation, liters per minute	8 9	15 7	31 0	26 8
Carbon dioxide output, percentage	2 21	2 49	2 42	2 39
Carbon dioxide output, cc per minute	197	390	750	641
Oxygen intake, percentage	3 02	3 75	2 83	2 77
Oxygen intake, cc per minute	270	590	877	743
Respiratory quotient	0 73	0 67	0 87	0 87
1 Minute, 37 Steps				
D—H B (normal)—11/28				
Respiratory rate	18	20	26	26
Tidal air, cc	417	805	980	604
Ventilation, liters per minute	7 5	16 1	25 5	15 7
Carbon dioxide output, percentage	2 48	3 68	3 13	3 33
Carbon dioxide output, cc per minute	186	592	799	523
Oxygen intake, percentage	3 69	5 87	3 96	4 60
Oxygen intake, cc per minute	277	945	1,010	722
Respiratory quotient	0 67	0 63	0 80	0 72

200 cc to 400 cc at this time, as compared with values before exercise. The measurements of the diameters of the chest are given in table 2.

Spirographic tracings of the dyspneic patient's respiration at rest, in fast and slow exercise and in recovery, together with comparative

tracings from the anoxemic and the normal subjects, are shown in figures 3 to 7. Exercise experiments were done with the dyspneic patient under normal basal conditions, other similar experiments when he was under the influence of epinephrine and still others after an injection of atropine. Measurements of the oxygen deficit were attempted

TABLE 4—*Respiratory Functions During Rest and During and After Four Minutes of "Slow" Exercise*

	Rest, Stand ing	Exercise (20 Steps per Minute)				Recovery	
		First Minute	Second Minute	Third Minute	Fourth Minute	First Minute	Second Minute
J M (dyspneic)—Experiments of 9/29, 9/30 and 10/2							
Respiratory rate	36 (26)* (11)		(16)	(16)	(16)	(22)	(30)
Tidal air, cc	323(481)	(868)	(1,257)	(1,265)	(1,298)	(1,162)	(790)
Ventilation, liters per minute	11.7	9.9	16.4	19.2	18.9	26.7	22.6
Carbon dioxide output, percent age	1.84	2.77	3.57	4.15	3.55	2.62	2.54
Carbon dioxide output, cc per minute	214	273	586	794	670	700	576
Oxygen intake, percentage	2.48	4.32	5.15	4.63	4.56	2.79	2.55
Oxygen intake, cc per minute	289	427	844	904	860	744	566
Respiratory quotient	0.74	0.64	0.70	0.80		0.94	1.01
A C (anoxemic)—Experiments of 11/3, 11/13 and 11/15							
Respiratory rate	24	25	30	32	27	41	
Tidal air, cc	470	696	712	845	1,120	764	
Ventilation, liters per minute	11.3	17.5	21.3	27.1	30.5	31.3	
Carbon dioxide output, percent age	2.05	2.46	2.68	3.06	3.32	2.85	
Carbon dioxide output, cc per minute	231	429	572	827	1,013	893	
Oxygen intake, percentage	2.76	3.36	3.63	3.61	3.45	3.03	
Oxygen intake, cc per minute	316	587	774	977	1,053	950	
Respiratory quotient	0.74	0.75	0.74	0.83	0.96	0.94	
H B (normal)—Experiments of 1/12 and 1/18							
Respiratory rate	19	19	20	21	20		
Tidal air, cc	428	640	975	955	1,227		
Ventilation, liters per minute	8.1	12.2	19.5	20.1	24.6	21.4	15.8
Carbon dioxide output, percent age	2.45	2.96	3.14	4.06	3.68	2.65	2.95
Carbon dioxide output, cc per minute	199	360	611	816	904	568	465
Oxygen intake, percentage	3.42	5.40	4.97	5.55	5.04	3.10	3.64
Oxygen intake, cc per minute	278	657	967	1,114	1,236	664	573
Respiratory quotient	0.72	0.55	0.64	0.73	0.74	0.86	0.79

\* From an experiment with graphic registration of respiration, with slightly increased resistance and therefore with slower respiratory rates.

on the dyspneic subject, without success on account of the variability in respiratory midposition. In the anoxemic subject the oxygen deficit was 250 cc and required five minutes to be replaced during oxygen breathing.

Examples of measurements of respiratory function during and after fast and slow exercise are given in tables 3 and 4. Similar experiments were done with the dyspneic subject after injections of atropine sulfate and of epinephrine hydrochloride.

Studies of the arterial blood at rest and immediately after one minute's exercise are shown in table 5

Simultaneous readings of venous pressure and pleural pressure are given in table 6

The arterial blood pressure was normal in both dyspneic and anoxemic patients at rest and showed normal responses after exercise. The

TABLE 5—Data on Arterial Blood During Rest and After Exercise

Subject	Date	Condition	Work, Number of Steps	Duration of Exercise, Minutes	Carbon Dioxide Volumes per Cent	Carbon Dioxide, Mm	pH	Arterial Blood			Oxygen Saturation, Percentage	Blood Volume, Cc	Blood Velocity, Seconds
								Oxygen, Volumes per Cent	Carbon Dioxide 10 Mm, Volumes per Cent	Oxygen Capacity, Volumes per Cent			
I M	8/9	At rest, fasting, supine	20	1	48.9	37.8	7.46	18.4	49.7	19.0	97	4,600	14
		Exercise 20 to 30 seconds after exercise			47.4	41.0	7.40	18.7	46.5	19.8	94		
	9/1	At rest, fasting, standing	25	1	48.0	36.5	7.44	19.9	49.3	20.0	95		
		Exercise 75 to 95 seconds after exercise			45.0	38.0	7.40	20.7	45.8	21.5	96		
A C	10/20	At rest, nonfasting, supine	37	1	51.8	39.3	7.44	14.7	51.3	16.4	88	4,100	13
		Exercise 20 to 40 seconds after exercise			47.5	44.5	7.37	14.9	44.5	17.4	86		
	11/24	At rest, fasting, standing	32	1	49.1	39.0	7.44		49.0	18.1			
		Exercise 60 to 90 seconds after exercise			45.2	42.3	7.39		43.3	19.2			
H B	11/21	At rest, nonfasting, supine	37	1	49.4	43.1	7.41		47.6	20.2			
		Exercise 55 to 75 seconds after exercise			46.1	43.4	7.39		44.1	21.0			

TABLE 6—Venous and Pleural Pressures

Condition	I M (dyspneic)			A C (anoxemic)		
	Date	Venous Pressure, Mm Water	Intrapleural Pressure, Cm Water	Date	Venous Pressure, Mm Water	
Quiet breathing	7/31/33	40	0, — 8	11/2	40	
Deep inspiration		43	—10		40	
Inspiration held		47	— 8		60	
Quiet breathing		38	0, — 8		40	
Deep expiration		55	+ 4		50	
Expiration held		59	+ 1		75	
Quiet breathing	7/26	60		11/2	40	
Hyperventilation		55			45	
Valsalva experiment		64			60+	
Rest	8/25	73				
Exercise 1 minute						
30 seconds later		110				
4 minutes later		76				
9 minutes later		61				
12 minutes later		73				

pulse rate was slightly high when the subjects were at rest but showed only moderate increase immediately after exercise and a rapid return to the resting level. In the early exercise experiments on the dyspneic subject the volume of the pulse (radial) determined by palpation was small immediately after exhausting (fast) exercise.

#### COMMENT

In a patient with normal circulation of the blood and a normal central nervous system the hydrogen ion concentration of the respiratory center is presumably dependent in part on the gases of the blood and on other acid-base relations in the arterial blood. For our three subjects these data are listed in table 5.

It will be noted that the exercise was not of exactly the same degree in all cases. The experiments with the dyspneic subject were done at a time when twenty or twenty-five steps a minute was the maximum that he could accomplish on account of extreme respiratory distress. Thus quantitative comparisons between the behavior of the three subjects cannot be made. Certain deductions, however, can be drawn. We assume that change in the value for carbon dioxide in the blood at a tension of 40 mm (i.e., in the level of the dissociation curve) was due primarily to the accumulation of lactic or other acid.

In brief, the data in table 5 show that the dyspnea which occurred with exercise in the first of the three subjects was associated with no oxygen unsaturation of the arterial blood and with only small changes in acidity and carbon dioxide tension of the blood, these changes being less than those which occurred after similar exercise in a patient (anoxemic) who was scarcely rendered dyspneic.

From the point of view of respiratory function, the studies of arterial blood in our dyspneic subject demonstrate clearly that aeration of blood in the lungs—the provision of sufficient breathing surface—was accomplished in a nearly normal manner. Furthermore, in efficiency of ventilation, this subject showed relatively little abnormality, as is illustrated in table 4, in the slow exercise experiments, the concentrations of carbon dioxide eliminated in the expired air and of oxygen absorbed were nearly the same in the dyspneic subject as in the normal. In fast exercise, the concentrations were less but were much higher than those in the anoxemic subject (table 3).

Disturbances in the mechanics of the circulation have been proposed as factors causing dyspnea in cardiac and pulmonary disease. Such are slowing of the cerebral circulation (Knipping<sup>13</sup>) and reflexes arising from elevated venous pressure (Harrison et al.<sup>12</sup>).

In view, however, of the normal responses of arterial and venous pressure in the dyspneic subject, the absence of accumulation of acid

in the blood, the increase in vital capacity after exercise and the brief duration of dyspnea after exercise had stopped, it seems unlikely that circulatory insufficiency was an important factor in the production of his dyspnea. Similarly, the normal vascular responses and the nearly normal amounts of the gases of the blood make it unlikely that stimulation of the carotid sinus plays a significant part in the abnormal pulmonary behavior in this subject (Heymans<sup>19</sup>).

Considered anatomically, the chest of the dyspneic subject was of the asthenic type, flat anteriorly (angle of Louis absent), with the upper part of the chest permanently elevated. There was kyphosis of the four upper dorsal vertebrae, the ribs were more horizontal than normal, the intercostal spaces were wide. Both diaphragms were at the same

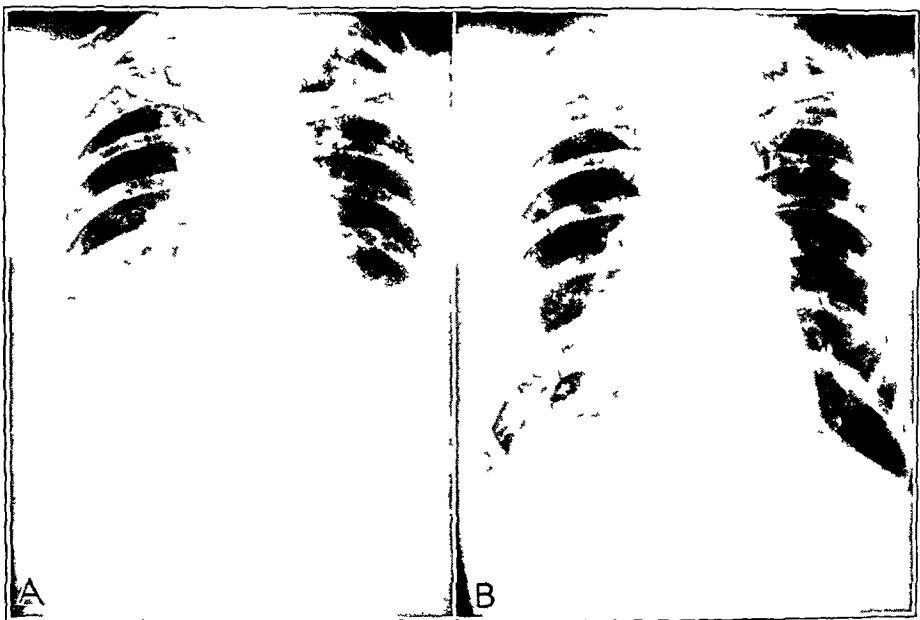


Fig 2—Roentgenograms of the chest (anteroposterior views) of the dyspneic subject, taken (A) in deep inspiration and (B) in deep expiration

level, low, and on lateral fluoroscopic view were seen to be flattened. Roentgenograms of the lungs taken at the end of expiration showed a marked increase in density in the lower parts of the lungs as compared with the density shown in films taken in inspiration (fig 2).

The outstanding characteristic respiratory movement, noticeable even during quiet breathing, was of the upper costal type described by Keith,<sup>20</sup> in its pathologically exaggerated form. During inspiration the

19 Heymans, C, Bouckaert, J J, and Regniers, P. Le sinus carotidien et la zone homologue cardio-aortique. Physiologie, pharmacologie, pathologie, clinique, Paris, Gaston Doin & Cie, 1933.

20 Keith, A, in Hill, L E. Further Advances in Physiology, London, Edward Arnold & Co, 1909.

sternocleidomastoid and the scalene muscles were markedly contracted, the shoulders moved upward and the depth of the suprasternal and subclavicular and supraclavicular fossae increased. The entire chest moved upward with no lateral expansion of the lower ribs. When the subject was in the supine as well as in the upright position, the abdomen was protruding. During expiration both sternocleidomastoid and scalene muscles remained hypertonically contracted, even while the entire anterior part of the chest moved downward (fig 1). In the patient's normal quiet respiration the diaphragm appeared tense, it flattened slightly during inspiration, its excursion at the most reaching 0.5 cm. The contraction of the upper respiratory muscles which are attached

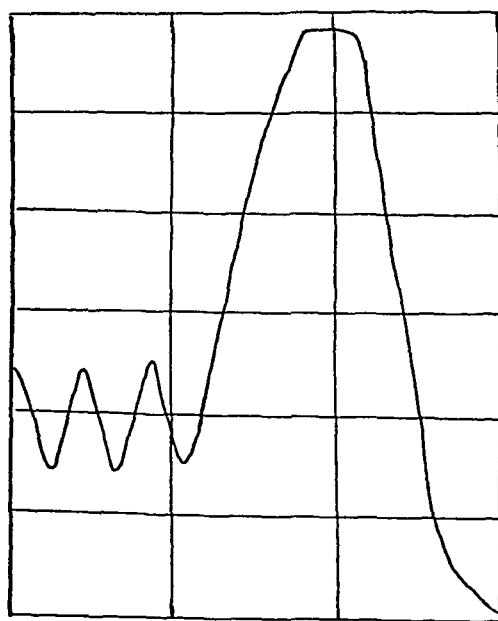


Fig 3—Tracing on the fast moving drum of quiet respiration and of the vital capacity of the dyspneic subject. The experiment was made on Sept 6, 1933.

around the six upper ribs, preceded any visible contraction of the diaphragm, the latter occupying only the latter part of the inspiratory cycle. Thus not only was there a predominance of the upper costal respiration, but what remained of the costodiaphragmatic respiration failed to synchronize with it.

In voluntary deep breathing, on the other hand, the excursion of the diaphragm reached from 4 to 5 cm (fig 2) and was continuous from complete inspiration to expiration. There was still, however, a persistence of the upper costal type of breathing.

As illustrated in figure 3 and in tables 3 and 4, measurements of quiet breathing of the dyspneic subject showed increased ventilation, rapid rate, small depth, variable midposition and, especially noteworthy, an increase of the time required for the inspiratory phase. This suggests



the type of breathing observed in obstruction of the air passages (Hess, Anthony) and is also like the respiration in patients with functional emphysema in attack-free periods described by Storm van Leeuwen, van Niekerk and Weltz<sup>15</sup>

Measurements of the volume of the lungs at rest showed a decrease in reserve and complemental air and a relative increase in residual air in both dyspneic and anoxemic subjects (table 1). On spirographic tracings (not shown in the figures) it was found that there was little difference in the volume of reserve air, whether the expiratory act started from the full inspiratory or from the normal expiratory position (Christie<sup>21</sup>).

Tracings of the pleural pressure synchronizing with a tracing of respiration (Christie) were not taken, but the data at our disposal on the dyspneic subject are sufficient to permit the drawing of some inferences as to the mechanical condition prevailing in the lung (table 6). The pleural pressure was higher than normal but was lower than that in persons with advanced emphysema. On quiet respiration it oscillated from -8 to 0, between deep inspiration and deep expiration, the difference in pressure averaged 14 cm. The level in quiet respiration was somewhat variable. When the breath was held after a deep inspiration, the pleural pressure increased only slightly from the maximum negative level. The evidence thus suggests that the elasticity of the lung tissue as a whole was moderately but not greatly impaired.

Summarizing the observations of the behavior of the dyspneic subject in the resting state, one may say that there is evidence of moderate loss of pulmonary elasticity, that normal quiet breathing was a hyperventilation almost wholly of the upper costal type, with evidence of some mechanical resistance to both inspiration and expiration, and that only in voluntary deep breathing were the muscles of the costodiaphragmatic group brought fully into play.

In untrained subjects there are likely to be irregularities in respiration at the beginning of exercise. These are well illustrated by figure 5, a tracing of the respiration of our normal control subject during rest, exercise and recovery. Although there was a striking constancy in the speed per unit of ventilating volume at which each respiration took place, his breathing showed much irregularity in rate and in the amplitude of individual respirations.

The breathing of the anoxemic subject (fig. 4, lower curve), on the other hand, showed during exercise only a sharp increase in rate, with relatively little alteration in amplitude. Each respiration was rapid

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21 Christie, R. V. The Elastic Properties of the Emphysematous Lung and Their Clinical Significance, *J. Clin. Investigation* **13** 295, 1934.

and was apparently accomplished without difficulty. Correspondingly, the exercise itself was performed with almost no dyspnea.

The type of breathing shown by the dyspneic subject during exercise is best illustrated by the upper tracing of figure 4, obtained during the patient's first few weeks in the hospital, and by the data in table 3. There are several distinctive features of this subject's breathing as shown by the spirographic tracings: 1. Most respirations during exer-

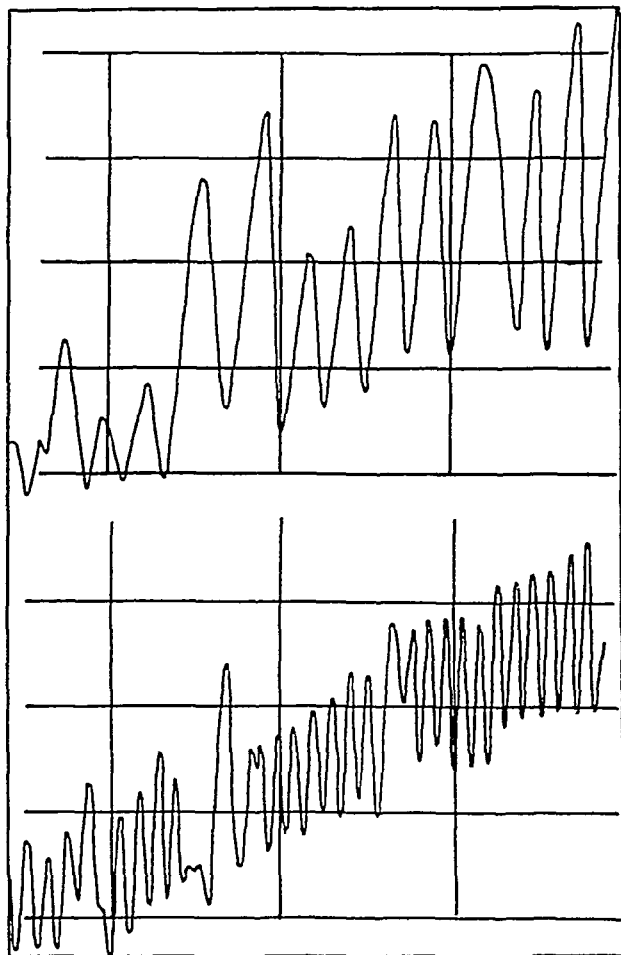


Fig 4—Tracings of respiration taken during one minute of fast exercise for the dyspneic subject above, experiment of Sept 9, 1933, and for the anoxic subject below, experiment of Oct 25, 1933.

cise, both the shallow and the deep ones, were greatly retarded throughout inspiration and expiration, suggesting an increased resistance to breathing. 2. There occurred now and then respirations of considerable amplitude (figs 4, 6 and 7), which were accomplished rapidly. 3. The amplitude of many respirations was large, suggesting the use of both the upper costal and the costodiaphragmatic musculature.

As a result of the retardation in respiration, the total pulmonary ventilation did not increase appreciably during the first minute of exer-

cise In fact, there was actually a decrease at times from the resting level (table 3) In spite of this, aeration of the blood was nearly adequate (table 5) This was probably due to the large breathing surface available in the deep respirations, even though the latter were slow

Subjectively, at the end of the minute of "fast" exercise, there developed an insupportable sense of distress and exhaustion, referred chiefly to the upper sternal region, which required cessation of the exercise

Equally striking were the changes that occurred in the dyspneic subject immediately after exercise had stopped (fig 6, table 3) The

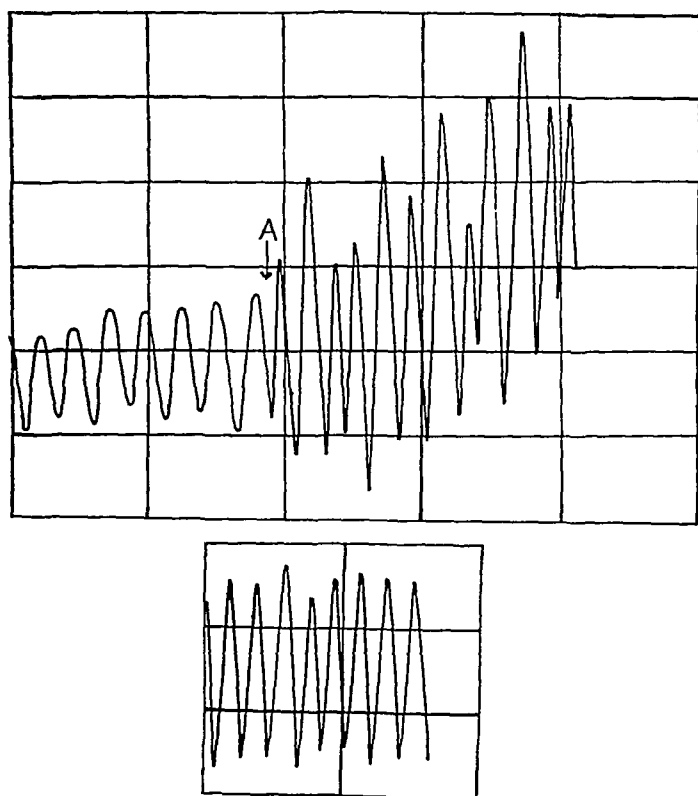


Fig 5—Tracings of the respiration of the normal subject showing successively respiration during rest, during a part of the first minute of exercise and during a part of the first minute of recovery (experiment of Oct 19, 1933) *A* indicates the beginning of the exercise

speed of the individual respiration increased immediately and to a marked degree, and respiration became rapid, regular and of average amplitude, so that the total pulmonary ventilation increased greatly Moreover, fluoroscopic examination at that time showed an increase of diaphragmatic excursion and a normal synchronization of the respiratory contraction of this muscle and of the muscles of the upper part of the chest The vital capacity was increased as compared with the

value obtained during resting before exercise. Subjectively, the sense of dyspnea disappeared rapidly, in less than two minutes.

During slow exercise (fig 7, table 4) the same phenomena were present at the beginning of exercise and during recovery. From the second to the end of the fourth minute, when exercise was proceeding in a nearly steady state, the respirations became regular and were of large amplitude. Each respiration was still retarded, but this effect became progressively less as exercise continued, so that the transition from exercise to recovery was not so marked as that after fast exercise, and the general behavior was more like that of the normal subject.

After injections of epinephrine hydrochloride (1 mg) sufficient to raise the blood pressure 20 mm, or of atropine sulfate (1 mg) sufficient to produce marked dryness of the mouth, fast and slow exercise experiments were carried out with the dyspneic subject. In all these the

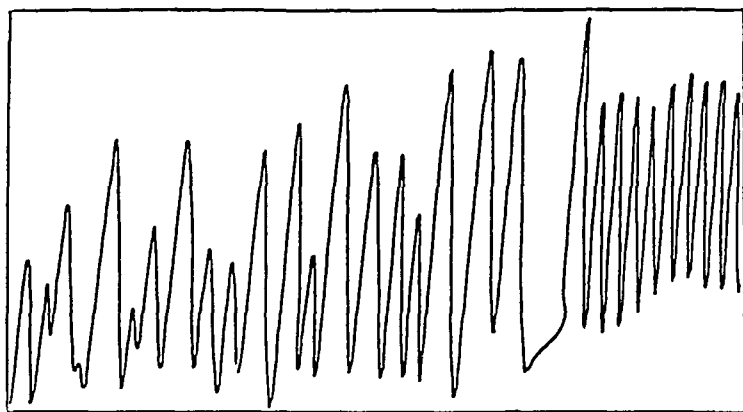


Fig 6—Tracing of the respiration of the dyspneic subject during one minute of exercise and the first part of recovery, fifteen minutes after the injection of 1 mg of atropine sulfate. The irregularly curved line at the end of one minute of exercise is an artefact due to the movement of the recording device just as the exercise stopped. The experiment was made on Oct 13, 1933.

results were essentially the same as those obtained when no drug had been given. Figure 6 shows a tracing made during fast exercise and recovery after the administration of atropine, figure 7, a tracing made during slow exercise and recovery after the administration of epinephrine.

In attempting to analyze the factors producing dyspnea in this patient, we start with the knowledge that he had moderately severe pulmonary fibrosis, producing emphysema in at least part of the lung fields and some loss of elasticity through the lungs generally. There may have been some obstruction of the air passages, though there was no definite evidence of this.

The difficulty of explaining the phenomena of respiration during exercise and recovery on the basis of either obstruction of air passages

or loss of pulmonary elasticity lies essentially in the abruptness with which, immediately after exercise had ceased, the respirations became rapid and even, using both the upper costal and the costodiaphragmatic muscles, especially when these were accomplished by the patient easily and without distress. It seems unlikely that the smooth muscle of lung or bronchial tissue would relax so quickly. The absence of effect of bronchodilator drugs on this whole respiratory pattern is also significant.

Even if one did suppose a sudden bronchial relaxation at the moment exercise stopped, one would still have the difficulty of explaining the not infrequent occasions, during the midst of exercise, when there occurred a single rapid and easy respiration (figs 4, 6 and 7). These

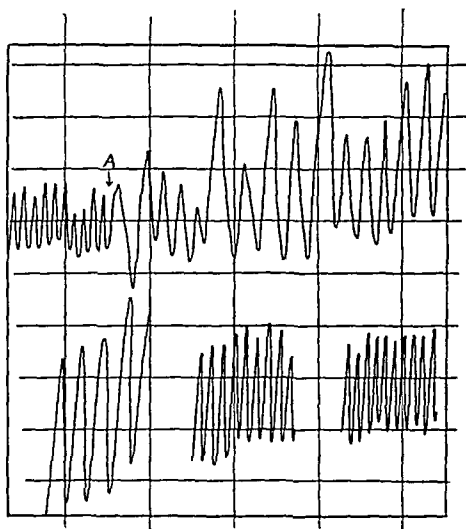


Fig 7—Tracings of the respiration of the dyspneic subject taken after an injection of 1 mg of epinephrine hydrochloride. The tracing shows successively (1) respiration during rest, (2) during the first minute of slow exercise, the exercise tracing beginning at *A*, (3) during part of the third minute of exercise, (4) during part of the first minute of recovery and (5) during part of the second minute of recovery. The experiment was made on Oct 5, 1933.

are the changes which one commonly sees in the activity of striated muscle.

The most reasonable explanation, in our opinion, is that the hypertonic state of the thoracic and diaphragmatic muscles themselves was a major factor restricting easy ventilation of the lungs in this case. Only in this way can we account for the rapidity of change of ventilatory function which we observed. There thus appears to have been, in the dyspneic subject, a factor of hypertonicity of the muscles of breathing, restricting costodiaphragmatic respiration at rest and retarding the whole respiratory act during exercise but to a great extent

released during the period of recovery. This explanation is all the more likely since we know, from observation of the patient (fig 1) and from fluoroscopic study, that spasm of the respiratory muscles was definitely present.

The sensation of dyspnea, or distress, associated with the act of breathing is presumably conveyed by proprioceptive impulses received from the moving framework of the chest and from the pulmonary tissues. The present study adds evidence to a more general concept that dyspnea is a sensation appearing whenever the mechanical apparatus for respiration is unable to provide easily the ventilation required by the person's immediate metabolic state but that dyspnea is essentially unrelated to the metabolic state as such.

We cannot, of course, be certain that the peculiar respiratory behavior observed in the dyspneic subject is connected with the pathologic condition in his lungs, but it seems highly probable that the hypertonic muscular state is conditioned by and dependent on the fibrosis and loss of elasticity in the lungs, through reflex mechanisms. How much the tonus and state of activity of the other bodily musculature during the stepping exercise have to do with the hypertonus of the breathing muscles can hardly be deduced from these limited observations.

The influence of a spastic state of the muscles, especially that of the diaphragm, in clinical dyspnea, has been recognized before, particularly in connection with corrective breathing exercises for asthmatic patients, such as those of Hofbauer<sup>22</sup> and Saenger<sup>23</sup>. These authors have emphasized, however, the effects on breathing of altered positions of the chest and of forms of movement, rather than the actual increased effort inherent in the ventilating movements performed with spastic muscles. Presumably the resistance to breathing in our subject was due primarily to failure of relaxation of antagonistic groups of muscles during any given movement, but there may have been other mechanisms.

The question may well be asked whether this whole dyspneic response was not a functional one or even actually a form of neurosis. Long continued observation of the patient made the latter seem highly unlikely, but even if it were true, it would be of secondary importance. Our observations have, we believe, provided an explanation of the immediate mechanism which rendered the patient's respiration difficult and subjectively distressing, it makes little difference for our present purpose what the psychologic background may have been.

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22 Hofbauer, L. Pathologische Physiologie der Atmung, in Bethe, A., von Bergmann, G., Emden, G., and Ellinger, A. Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1925, vol 2, p 337.

23 Saenger, M. Ueber Asthma und seine Behandlung, Berlin, S. Karger, 1910.

The effect of repeated exercises on abnormal muscular states relates them immediately to the phenomenon of muscular training. The respiratory act is to be considered as a part of all training in general bodily exertion, the attainment of a given exchange of gases at adequate tensions with a minimum of respiratory effort. In this sense the case of our dyspneic subject may be considered as an example of pathologically subnormal training in respiratory behavior. A further evidence for this point of view is the rather remarkable improvement that occurred in the dyspneic subject's respiratory function as well as in his tolerance of exercise during the course of several months of exercise experiments. The form of respiratory tracing at the end of that time was practically the same as that for the normal subject (fig 5).

There is no reason to suppose that a spastic muscular state is regularly of primary importance in the dyspnea associated with pulmonary fibrosis. On the other hand, it is likely that there are numerous phases of pulmonary insufficiency of various kinds in which such a state plays an important part. The disturbance in the case we have described is analogous to several clinical conditions or groups of conditions that have been reported recently, such as the hypertonicity of the diaphragm studied by Patzold<sup>24</sup> in cases of artificial pneumothorax in asthenic persons or the muscular fixation of the chest in persons with asthma described by Klewitz<sup>25</sup>. The two patients of Ruettgers<sup>26</sup> who had subjective dyspnea in spite of a good efficiency coefficient may also have had a malady similar to that of our dyspneic subject. The "functional emphysema" of Stoim van Leeuwen, van Niekerk and Weltz<sup>15</sup> presents many similarities.

#### SUMMARY

The purpose of this paper has been to show that in one particular form of pulmonary fibrosis, dyspnea during mild exertion was apparently due in large part to a hypertonic state of the respiratory muscles and to a disturbance of the normal synergic relations between various groups of them. If our deductions are correct, this disturbance of action of the muscles of respiration takes its place among the numerous other factors which contribute to the causation of dyspnea and adds further to the general concept of dyspnea as a subjective sensation brought on whenever the mechanical apparatus for respiration is unable to provide easily the pulmonary ventilation required by the person's immediate physicochemical and metabolic state.

24 Patzold, A. Die Gestaltung der Atemökonomie unter Pneumothoraxbehandlung, *Ztschr f Tuberk* **69** 172, 1933.

25 Klewitz, Felix. Das Bronchialasthma, in Grote, L. R., Fromme, A., and Warnekros, K. *Medizinische Praxis*, Dresden, Theodor Steinkopff, 1928, vol. 3.

26 Ruettgers, I. Untersuchungen über die Arbeitsökonomie bei Lungentuberkulosen, *Beitr z Klin d Tuberk* **78** 197, 1931.

# DAILY VARIATION OF SUGAR CONTENT OF BLOOD AND URINE DURING TREATMENT OF DIABETES MELLITUS

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LINCOLN, NEB

It is not unusual to observe that a diabetic patient excretes large amounts of sugar before breakfast whereas the urine is sugar-free or nearly so during the remainder of the day. It is well known that reactions to insulin are more common during the afternoon or evening than at other times of the day, provided the amounts of insulin taken before meals are similar. In order to keep diabetic patients sugar-free, particularly the ones with severe diabetes, it is often necessary to give more insulin in the morning than at noon or at night.

The curves for the blood sugar and the sugar excreted following the dextrose test meal suggest the use of insulin before each meal and lead one to expect similar results from like amounts of insulin regardless of time of day. The previously mentioned observations indicate that this expectation is not uniformly met. Apparently the postprandial rise in the blood sugar level is not uniform after the three meals of the day. If it were, insulin would be no more likely to cause reactions in the afternoon than in the morning, and more insulin would not be needed to control the metabolism of sugar during the morning than during the afternoon. The postprandial rise in the blood sugar level does not explain the excretion of larger amounts of sugar before the morning meal. Apparently there is some daily variation in the metabolism of sugar, as suggested by Mollerstrom,<sup>1</sup> who called attention to a periodicity in the metabolism of carbohydrate, emphasizing the work of Forsgren, who held that the liver functions alternately in the storage of glycogen and the secretion of bile. Sprague and Newson<sup>2</sup> recently reported a case in which there was marked daily variation in the amount of blood sugar, which was controlled by administering the morning dose of insulin at an early hour.

With the question of the daily variation in the sugar content of the blood and in the amount of excreted sugar in mind, I have studied during the past three years twenty-four patients with diabetes. These

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1 Mollerstrom, J. Periodicity of Carbohydrate Metabolism and Rhythmic Functioning of the Liver, *Arch Int Med* **52** 649 (Nov) 1933.

2 Sprague, P. H., and Newson, D. A. Study of Twenty-Four Hour Blood Sugar Curve in Diabetic Patients, *Canad M A J* **31** 609 (Dec) 1934.



patients were definitely diabetic with various degrees of severity and were of various ages. For the most part they were free from complications or associated diseases. The study was carried out in the following manner:

The patients were hospitalized without restricting their activity. They were placed on a weighed adequate diet. As a rule the carbohydrate exceeded the fat by one-fourth, measured in grams. Insulin, when indicated, was given fifteen minutes before meals in amounts estimated to render the patient nearly sugar-free. This treatment was maintained for a number of days to establish stability. Then the blood sugar content was determined every four hours and also the amount of sugar excreted during the four hours. The tests were made at the four hour intervals throughout the twenty-four hours of the day. The patients were studied in this manner for from two to twelve days. Folin's method was used in determinations of the sugar in the blood and the sugar in the urine was measured by Benedict's method.

Approximately half of the patients showed a definite daily variability in the amount of blood sugar and in the amount of sugar excreted. This consisted in an increase of both, starting soon after midnight and lasting until near noon. Lower levels were found during the afternoon and the early part of the night. In those cases in which marked variability was shown a change was made in the timing of the doses of insulin. This proved very effective in controlling both hyperglycemia and glycosuria otherwise difficult to control.

The cases noted in the following paragraphs and the accompanying charts are typical.

#### REPORT OF CASES

CASE 1—A girl, L. B., 12 years of age, had had diabetes for five years. During the previous year she had had many reactions to insulin and twice had been in diabetic coma. Chart 1 shows that on doses of 50, 15 and 17 units of insulin given fifteen minutes before meals the blood sugar content varied daily from 100 to 400 mg and the amount of excreted sugar during the four hour periods from none to 30 Gm. On the fourth day the 50 unit dose of insulin was given at 4 instead of at 7:45 a. m., or four hours instead of fifteen minutes before breakfast. This was in anticipation of the peak at 8 o'clock. No change in the time of administering the other doses of insulin was made as the curve indicated satisfactory control by these doses. In chart 1 the blood sugar curve and the shaded columns showing the amount of sugar excreted indicate a more constant control following the change. This method of administering insulin has been continued, and in the fourteen months of observation since this study the patient has shown remarkable improvement.

CASE 2—A man, W. C., 54 years of age, had had diabetes for seven years and had taken insulin for two years. He had no complaints except that he almost constantly had sugar in the urine. Chart 2 shows no definite daily variation in the blood sugar or in the sugar excreted. Observation following this study shows that after the insulin was increased from two daily doses of 15 and 5 units to three doses of 20, 5 and 10 units, his blood and urine became constantly sugar-free.

CASE 3—A boy, G. M., 10 years of age, had had severe diabetes for three years. He had taken insulin during the three years and had had many reactions, often had sugar in the urine and twice had been in coma. Chart 3 shows a daily variation similar to that in chart 1. Following a change in the time of administering insulin, which was similar to the change indicated in chart 1,

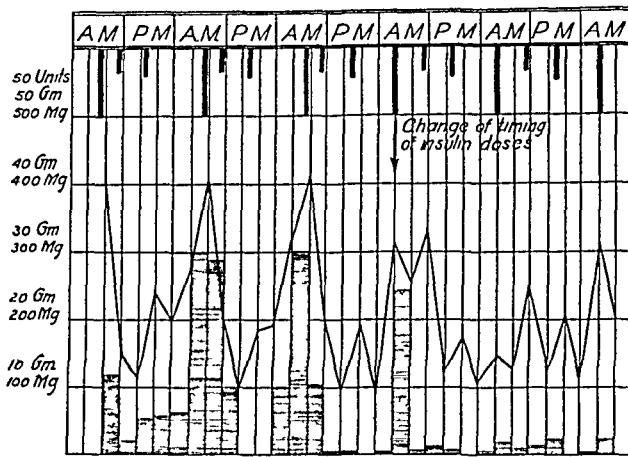


Chart 1 (case 1) —The curves show that when the patient receives doses of 50, 15 and 17 units of insulin taken fifteen minutes before meals the blood sugar varied daily from 400 to 100 mg and the sugar excreted during the four hour periods from 30 Gm to none, and that more satisfactory results were obtained on administering the insulin four hours before breakfast. In this and the succeeding charts the solid black columns represent the doses of insulin, the shaded columns, the dextrose in the urine, and the black line, the blood sugar.

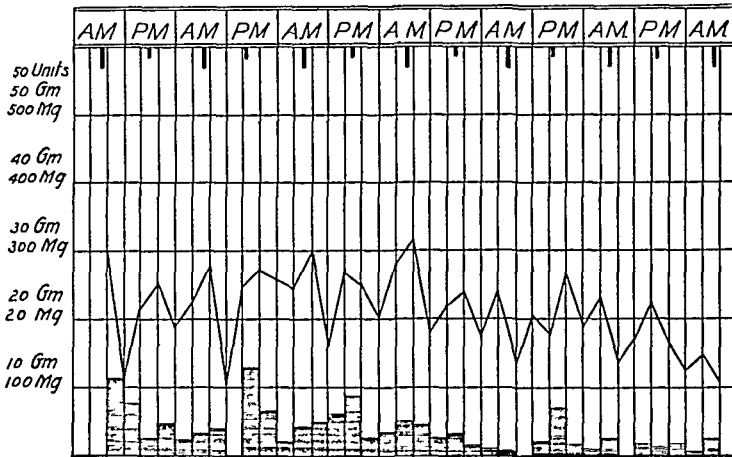


Chart 2 (case 2) —The curves show no definite daily variation in the blood sugar or in the sugar excreted.

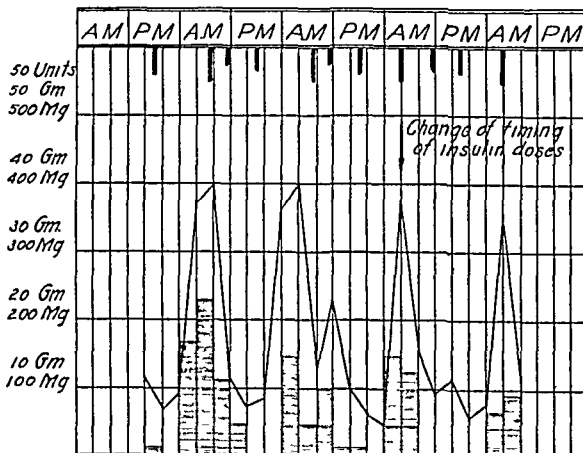


Chart 3 (case 3) —The curves show a daily variation similar to that seen in chart 1.

there was one instead of two high blood sugar readings during the day, and the excretion of sugar decreased. The adjustment in the timing of the doses of insulin has not been sufficient to control the variability.

Chart 4 shows the blood sugar and urinary sugar of the same patient one year later. The patient had not followed directions well during the year, the diabetes evidently was more severe, and larger amounts of insulin were being given. The chart shows that until the first change in the administration of insulin, which was made on the third day, the blood and urinary sugar were characterized by a daily variation similar to that in the previous study. Until noon of the third day he was given insulin fifteen minutes before meals in doses of 40, 20 and 30 units. He was given no insulin at noon or at night on the third day and was given 70 units at 2 a. m. the following morning. I wished to know if one dose given in anticipation of the morning peak would control the condition throughout the day. The chart shows a sharp rise in the blood sugar level to 420 mg. and as much as 32 Gm. of sugar in the urine during the four hour period in the evening when insulin was omitted. The 70 unit dose caused a fall in the blood sugar in

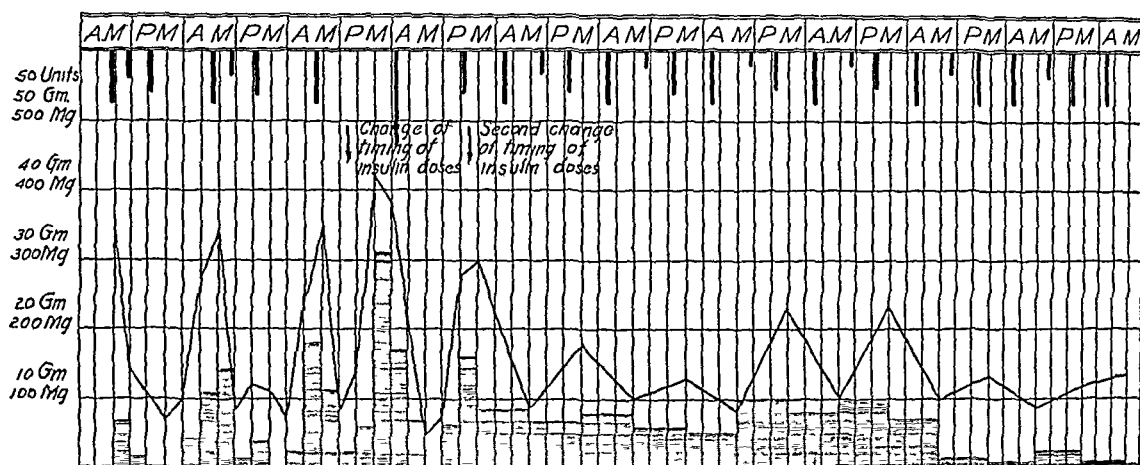


Chart 4 (case 3) —Curves made one year after those shown in chart 3

the morning to 50 mg. and a sharp reaction. Evidently a single dose would not control the condition of this patient throughout the day. The second change in the administration of insulin was to give 40, 20 and 30 units, or the same amounts as given during the first two days, with the first dose at 2 a. m. to anticipate the peak. This resulted in more constant control of the blood sugar content and of the amount of sugar excreted. A needed increase in diet on the seventh day resulted in an increase in the blood sugar content during the seventh and eighth evenings. An increase of the evening dose of insulin from 30 to 40 units resulted in maintenance of control of the blood sugar and of the sugar excreted.

#### SUMMARY

A study of twenty-four cases of diabetes mellitus with regard to a daily quantitative variation in sugar content of the blood and in the amount of sugar excreted showed such a variation in sixteen cases. In nine cases the variation was slight, in seven it was marked enough to interfere with satisfactory treatment when the injections of insulin

were given before meals. The variation consisted in an early morning rise in the blood sugar content, a parallel rise in the amount of sugar excreted and an afternoon fall in both. Meals did not seem to affect the curves. As a rule the variation was found in young patients with severe diabetes, while older patients with milder forms of the disease often failed to show it.

The administration of insulin in anticipation of the early morning rise has resulted in more satisfactory control than could be obtained otherwise, but there was no evidence that the total requirement of insulin could be reduced by this method of administration, as stressed by Mollerstrom. A single dose of insulin given in anticipation of the peak failed to control the condition adequately throughout the twenty-four hours.

One patient showing the variation was restudied after a year, and similar variability was found, indicating permanence.

A single estimation of blood sugar, regardless of the time of day, gives incomplete information and may be misleading.

Accurate establishment of the existence of a definite and constant early morning rise in the blood sugar level should always precede the giving of large doses of insulin in the early morning.

# PRESENCE IN NORMAL HUMAN URINE OF A RETICULOCYTE-STIMULATING PRINCIPLE FOR THE PIGEON

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Recent experimental work on the etiology of pernicious anemia points to the formation in normal persons of an erythrogenic principle by the interaction of gastric juice and certain dietary constituents, subsequent absorption of the principle and storage in the liver. This process is well known to be grossly deficient in persons with pernicious anemia<sup>1</sup>. In normal persons it appears that a sufficient concentration of this hematogenic principle is maintained in the blood stream to effect the normal maturation of the red blood cells in the bone marrow. The logic of examining urine for the presence of the hematogenic principle is therefore apparent. Moreover, renal tissue has already been shown to contain an appreciable amount of the principle acting against pernicious anemia<sup>2</sup>. This report deals with preliminary observations relative to the presence in normal human urine of a substance which is perhaps identical with the hematogenic or antianemia principle present in the liver.

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From the Department of Physiology and Pharmacology, University of Louisville School of Medicine

This research was aided by a grant from the Committee on Therapeutic Research of the American Medical Association

1 (a) Castle, W B. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *Am J M Sc* **178** 748, 1929. (b) Ivy, A C, Richter, O, and Kim, M S. Some Experiments Bearing on the Etiology of Pernicious Anemia, *Am J Physiol* **101** 59, 1932. (c) Wilkinson, J F, and Klein, L. The Relationship Between the Anti-Anaemic Principles in Stomach and Liver, *Lancet* **2** 629, 1933. (d) Singer, C. The Theoretical and Practical Importance of the Depot Effect of the Antiperniciosa Principle, *Wien klin Wchnschr* **46** 619, 1933. (e) Isaacs, R, and Goldhamer, S M. Rôle of Decreased Amount of Gastric Secretion in Production of Pernicious Anemia, *Proc Soc Exper Biol & Med* **31** 706, 1934. (f) Bence, J. Rôle of Stomach and Liver in Pathology of Pernicious Anemia, *Ztschr f klin Med* **126** 127, 1933. (g) Wilkinson, J F, and Klein, L. Hematopoietic Activity of the Normal and Abnormal Human Liver with Especial Reference to Pernicious Anemia, *Quart J Med* **3** 341, 1934. (h) Goodman, L, Geiger, A J, and Claiborn, L N. Anti-Anemia Potency of Liver After Gastrectomy in Swine, *Proc Soc Exper Biol & Med* **32** 810, 1935.

2 McCann, W S. Effect of Kidney on Blood Regeneration in Pernicious Anemia, *Proc Soc Exper Biol & Med* **25** 255, 1928.

## METHOD

The procedure employed for studying the possible presence of the erythrocytic principle in human urine was basically the pigeon method already reported on by Vaughan, Muller and Zetzel,<sup>3</sup> as well as others.<sup>4</sup> The objections to this method<sup>5</sup> we have largely obviated by certain modifications, which will be published in detail shortly.

Suffice it to say here that staining with brilliant cresyl blue by the wet smear technic shows the cytoplasm of practically all (from 97 to 99 per cent) of the red blood cells of the pigeon to contain reticular material varying from one granule to a fairly complete filling of the cytoplasm. The red blood cells of the pigeon were therefore divided into three groups: (1) nonreticulated and slightly reticulated cells, (2) moderately reticulated cells and (3) heavily reticulated cells. Although there are no sharp lines of demarcation between these groups, a little practice enables one to make a satisfactory separation. All the counts on any one bird were, of course, made by one person, although numerous duplicate counts by both of us showed close agreement. For the purposes of this report, the cells of groups 2 and 3 are combined and arbitrarily called reticulocytes and those of group 1 are considered nonreticulocytes.

Daily reticulocyte counts were made on twenty-four untreated, grain-fed pigeons weighing from 350 to 500 Gm each, for eight weeks. The maximum reticulocyte counts of the birds during the period specified were as follows: nineteen pigeons, 15 per cent or less, one pigeon, 17 per cent, two pigeons, 18 per cent, one pigeon, 20 per cent, and one pigeon, 27 per cent. Only one of the birds of this control series, therefore, showed a spontaneous rise in the percentage of reticulocytes, the count increasing to more than 20 per cent during the eight week period. These observations are summarized in table 1. The minimum reticulocyte counts for these control pigeons were as follows: nineteen pigeons, 7 per cent or more, three pigeons, 6 per cent, and two pigeons, 5 per cent.

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3 Vaughan, J. M., Muller, G. L., and Zetzel, L. The Response of Grain-Fed Pigeons to Substances Effective in Pernicious Anemia, *Brit J Exper Path* **11** 456, 1930.

4 (a) Muller, G. L. The Influence of Liver Extract and Acute Infection on Reticulocytes and Bone Marrow of Pigeons, *Proc Soc Exper Biol & Med* **29** 151, 1931. (b) Edmunds, C. W., and Brueckner, H. H. Some Laboratory Experiments with Liver Extracts, *J Pharmacol & Exper Therap* **45** 258, 1932. (c) Edmunds, C. W., Brueckner, H. H., and Fritzell, A. I. On a Laboratory Test for Liver Extracts, *J Am Pharm A* **22** 91, 1933. (d) Peabody, W. A., and Neale, R. C. The Pigeon as a Hematopoietic Test Animal, *ibid* **22** 1231, 1933.

5 Wills, L. Spontaneous Fluctuations in the Reticulocyte Count in Pigeon's Blood, *Brit J Exper Path* **13** 172, 1932. Heimann, H., Connery, J. E., and Goldwater, L. J. Lack of Effect of Liver Treatment on the Circulating Reticulocytes in the Pigeon, *Am J M Sc* **188** 343, 1934.

Like other workers, we found that the intramuscular administration of a potent liver extract for parenteral administration<sup>6</sup> (3 cc equivalent to 100 Gm of liver) in doses of 0.05, 0.1, 0.2, 0.3, and 0.6 cc daily for five days to ten pigeons (two birds receiving each amount) caused a significant increase in the percentage of reticulocytes, the count increasing to more than 20 per cent, in the six birds receiving the 0.2, 0.3 and 0.6 cc doses. The maximal significant increase in the percentage of reticulocytes in the latter occurred on the average eleven days after the first injection, the extremes being eight and seventeen days. The results obtained with this liver extract are summarized in table 2. These results, as well as others obtained with two additional liver preparations for parenteral administration<sup>7</sup> indicate that in sufficient dosage administration to pigeons of the hematogenic principle present in the liver causes an increase of the percentage of

TABLE 1—*Maximum Reticulocyte Counts of Twenty-Four Untreated Pigeons During an Eight Week Period of Observation\**

Maximum Percentage of Reticulocytes	Number of Pigeons	Maximum Percentage of Reticulocytes	Number of Pigeons
10	1	15	1
11	5	17	1
12	3	18	2
13	6	20	1
14	3	27	1

\* Daily counts were made

TABLE 2—*The Effect of Parenteral Liver Extract on the Reticulocyte Counts of Ten Pigeons*

Dose in Cc per Pigeon Injected Intramuscularly for Five Successive Days									
0.05		0.1		0.2		0.3		0.6	
(16%)	(15%)	(17%)	(14%)	+	+	+	+	+	+
				(22%)	(23%)	(21%)	(27%)	(29%)	(30%)

+ denotes an increase in reticulocytes to a significant level, viz, more than 20 per cent, after injections, denotes no increase in reticulocytes to a significant level. The maximum percentage of reticulocytes for each pigeon after the injections is given in parenthesis

reticulocytes to more than 20 in all birds, whereas only approximately 4 per cent of untreated pigeons show a spontaneous increase of the reticulocyte count to more than 20 per cent in a corresponding period. The chart shows the daily reticulocyte counts of one of the two pigeons which received the 0.6 cc doses of liver extract and the counts of a typical control bird.

To test for the possible presence of the erythrogenic principle in human urine, sterile morning specimens were obtained from six normal persons (three men and three women) ranging in age from 20 to 35 years. Eight pigeons were used for the urine of each subject. Four of the birds received intramuscular injections of 0.1, 0.5, 1.0, and 1.5 cc of unheated urine per hundred grams of body weight,

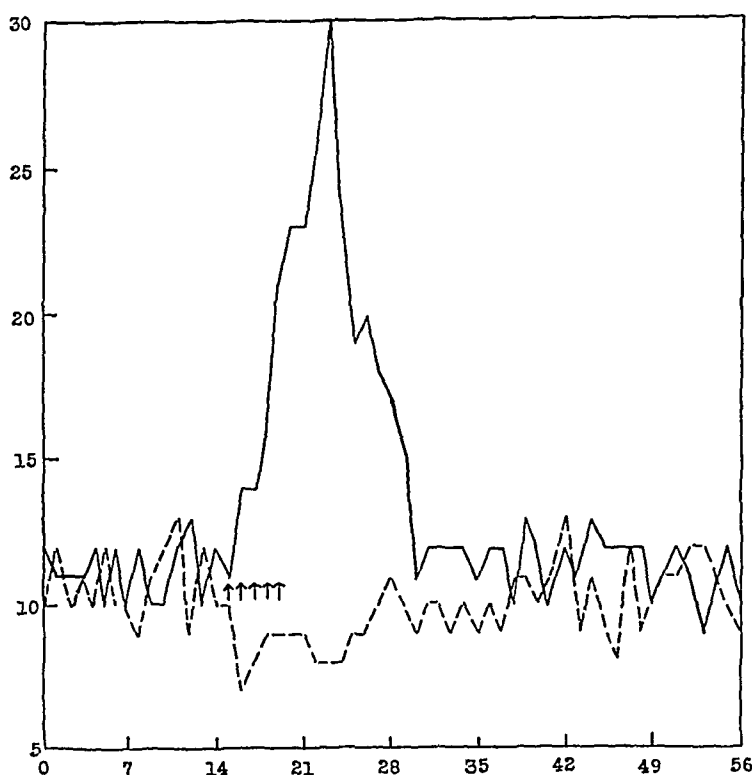
6 This preparation was supplied by Dr. Guy W. Clark of the Lederle Laboratories, Pearl River, N. Y.

7 These preparations were supplied by the Abbott Laboratories, North Chicago, Ill., and Dr. J. D. Ralston, of Parke, Davis & Co., Detroit, Mich.

respectively, for five successive days. The other four birds received corresponding amounts of urine previously heated to 100 C for two hours. The urine from the second and from the third man (table 3) was heated and subjected to free access of air, the urine from the other four persons was heated without free access of air. Daily reticulocyte counts were made for two weeks before the injections and for six weeks after the first injection.

### RESULTS

The unheated urine from the three men produced an increase in reticulocytes to more than 20 per cent in nine of the twelve birds which received injections (table 3). In tests with the urine of the first man the significant increase was evident with all four doses, in tests with



Effect of parenteral liver extract on the reticulocyte count of pigeons. Counts were made daily. The figures on the horizontal axis indicate the time in days, those on the vertical axis, the percentage of reticulocytes. The solid line represents the counts for the pigeon receiving liver extract, the broken line, the counts for the untreated pigeon. The arrows indicate intramuscular injections of 0.6 cc of liver extract prepared for parenteral administration.

the urine of the second man it was evident with the three largest doses, and in tests with the urine of the third man it was evident with the two largest doses. Moreover, as is apparent from table 3, the remaining three birds gave what may, in the light of the observations on the control pigeons (table 1), be interpreted as a partial response, although on the basis of the established critical reticulocyte level of 20 per cent,



the results in these birds are considered as negative. There was no increase to more than 20 per cent in the twelve pigeons which received injections of the heated urine of the three men. However, the results with the urine from the first man indicate that its reticulocyte-stimulating activity was not completely destroyed by the heat treatment. The urine of the second and of the third man, which was subjected to heat treatment with free access of air, however, showed no reticulocyte-stimulating activity in the doses employed (table 3).

The unheated urine from the three women produced a significant increase, namely to more than 20 per cent, in the number of reticulocytes of eight of the twelve birds which received injections (table 3).

TABLE 3—*The Effect of Normal Human Urine on the Reticulocyte Counts of Forty-Eight Pigeons*

	Urine	Unheated Urine				Heated Urine			
		Dose in Cc per 100 Gm of Body Weight*				Dose in Cc per 100 Gm of Body Weight*			
		0.1	0.5	1.0	1.5	0.1	0.5	1.0	1.5
Male	1	+	+	+	+	(15%)	(20%)	(15%)	(17%)
		(26%)	(28%)	(23%)	(34%)				
	2	(16%)	+	+	+	(12%)	(15%)	(13%)	(12%)
			(26%)	(25%)	(27%)				
	3	(17%)	(19%)	+	+	(12%)	(13%)	(12%)	(17%)
				(37%)	(39%)				
Female	1	+	+	+	+	(18%)	(17%)	(20%)	(16%)
		(26%)	(21%)	(32%)	(34%)				
	2	+	+	+	+	(15%)	(20%)	+	+
		(49%)	(16%)	(39%)	(38%)			(28%)	(33%)
	3	(18%)	(15%)	(18%)	+	(16%)	+	(13%)	(14%)
					(23%)		(21%)		

\* Urine was injected intramuscularly for five successive days. + denotes an increase in reticulocytes to a significant level, viz., to more than 20 per cent. denotes no increase in the percentage of reticulocytes to a significant level. The maximum percentage of reticulocytes for each pigeon after the injections is given in parenthesis.

In tests with the urine from the first woman the increase was evident with all four doses, in tests with the urine of the second woman it was evident with the smallest and with the two largest doses, and in tests with urine from the third woman it was evident only with the largest dose. Again, the results in the four remaining birds may be considered to represent a partial response. Nine of the twelve birds which received injections of the heated urine of women did not show a significant increase in the percentage of reticulocytes, although the maximum counts in some of these birds indicated an incomplete destruction of reticulocyte-stimulating activity by the heat treatment. Of the remaining three birds which did show an increase above 20 per cent in the reticulocyte count, two received 1 cc and 1.5 cc doses of the urine from the second woman, and the third received 0.5 cc doses of the urine from the third woman.

The maximal significant increases in the reticulocyte count produced by the unheated and heated urine occurred on an average fifteen days after the first injection, the extremes being six and twenty days

#### COMMENT

Whereas one (4 per cent) of twenty-four birds which did not receive injections and three (13 per cent) of twenty-four birds which received injections of various doses of the heated urine of the six persons showed a subsequent reticulocyte count of more than 20 per cent, seventeen (71 per cent) of twenty-four birds which received injections of various doses of the unheated urine and six (60 per cent) of ten pigeons which received injections of various amounts of an active liver extract showed significant increases in the reticulocyte count. These results point to the presence in normal human urine of a substance which increases the amount of the reticular material in the blood cells of the pigeon as does the hematogenic principle present in liver. From the roughly quantitative data presented, it is apparent that the amount of the reticulocyte-stimulating substance in the average normal human urine is approximately one tenth of the concentration of the reticulocyte-stimulating principle present in the aforementioned liver extract for parenteral administration. It is also apparent that the amount of this material in the urine of different normal persons varies from one person to another. Moreover, pigeons differ somewhat (without relationship to sex) in their sensitiveness to the reticulocyte-stimulating material, although there is a certain degree of proportion between the amount of the urinary and hepatic principles injected and the magnitude, as well as the rapidity of onset, of the response of the reticulocytes.

There are some facts which point to at least a similarity, and possibly an identity, of this urinary substance and the principle in the liver that acts against pernicious anemia. Thus, as already stated, the urinary substance is partially thermostable. This is also true of the liver principle.<sup>8</sup> Furthermore, the reticulocyte-stimulating urinary substance is more readily destroyed by heat in the presence of air, and a free access of air has been reported to exert a destructive action on the erythrogenic principle present in the liver.<sup>4c</sup> By means of a procedure somewhat similar to that used for the antianemia principle present in the liver we have extracted the urinary substance from normal human urine and have found this concentrated extract active by the pigeon method. The urinary principle, like the hepatic principle, is nonvolatile at body temperature, relatively soluble in 70 per cent ethyl alcohol, and relatively insoluble in 95 per cent ethyl alcohol. We shall shortly attempt to con-

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<sup>8</sup> Clark, G. W. Personal communication to the authors. Ralston, J. D. Personal communication to the authors. Wilkinson and Klein.<sup>1c</sup>

firm the presence of this apparent erythrogenic principle in normal human urine by the guinea-pig method of Jacobson<sup>9</sup> As soon as suitable patients with pernicious anemia are available, we shall test the erythrogenic properties of the urinary extract in man

#### SUMMARY

A modification of the pigeon method for gaging the potency of preparations for the combating of pernicious anemia is briefly outlined

Normal human urine contains a substance which significantly increases the amount of reticular material in the red blood cells of the pigeon, as does also the erythropoietic principle present in liver<sup>10</sup>

Like the latter, the urinary substance is partially thermostable Other evidence is presented pointing to at least a similarity and possibly an identity of the urinary and hepatic principles

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9 Jacobson, B M The Response of the Normal Guinea Pig to the Administration of Liver Extracts, *Science* **80** 211, 1934

10 Since the completion of this work Decastello (*Med Klin* **31** 377, 1935) reported that normal human urine was effective when administered rectally to patients with pernicious anemia Later Leiner (*Wien klin Wchnschr* **48** 559, 1935) and Walters (*Proc Am Physiol Soc*, 1936, p 158) found normal human urine to be reticulocytogenic for the rat and guinea-pig, respectively

# Progress in Internal Medicine

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## LIVER AND BILIARY TRACT

A REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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Progress in medicine is variable both as to speed and as to the different fields involved. Medical knowledge of diseases of the gallbladder may be said to date from the fourteenth century, when the observation of gallstones at necropsy was first reported. The study of cholecystitis has been limited to the past century, while detailed knowledge of the normal function of the gallbladder has been obtained only within the past decade or two. A better understanding of the normal function of the gallbladder, on the other hand, has necessitated a revision of the theories regarding the pathogenesis of both cholecystitis and cholelithiasis.

### PHYSIOLOGY OF THE GALLBLADDER

The present views regarding the normal physiologic activity of the gallbladder were summarized in the last review<sup>1</sup> and need not be repeated. During the past year there have been no significant changes in these views.

Biliary colic with pain radiating from the epigastrium to the right shoulder or the back represents one of the classic examples of referred pain. The mechanism of such referred visceral pain has been variously explained. The theory of Mackenzie does not recognize visceral pain as such but assumes that pain impulses arising from the gallbladder or the common bile duct travel to the cord by way of the celiac ganglion and the right splanchnic nerves. These sympathetic impulses sensitize the segment of the cord which they enter so that the ordinary somatic sensory impulses are appreciated as pain. This viscerosensory mechanism is assumed to be responsible for pain referred to the epigastrium or to the back in cholelithiasis. The theory of Moiley assumes that an abnormal tension on the muscular walls of the hollow viscera gives rise to a true visceral pain. This is a deep-seated central pain,

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From the Clinic for Diseases of the Liver and Biliary Tract of the Departments of Medicine and Surgery, the New York Post-Graduate Medical School and Hospital.

1. Greene, C. H., Bercovitz, Z., and Hanssen, E. C. Liver and Biliary Tract. Review of the Literature of 1933 and 1934, *Arch. Int. Med.* **55**: 681 (April) 1935.

is not accurately localized and does not radiate. The parietal peritoneum is innervated by the somatic spinal nerves and is highly sensitive. These nerves extend into the gastrohepatic omentum for a variable distance, so inflammation of the extrahepatic bile ducts may give rise to such peritoneocutaneous radiation of pain to the back.

Zollinger and Young<sup>2</sup> attempted to determine the relative merits of these two theories by mechanically distending the gallbladder or common duct of conscious patients. Nine cases were studied. At the time of operation the gallbladder or common duct was exposed with the patient under local or gas-oxygen anesthesia. The stones were removed from the gallbladder or common duct, and a sterile balloon was inserted. When the patient had recovered from the anesthesia sufficiently to answer questions intelligently, the balloon was distended and the signs and symptoms were noted. Zollinger reports as follows: 1 Mechanical distention of the gallbladder usually gave rise to deep epigastric discomfort similar to the attacks of indigestion in cholecystitis but more severe. 2 The discomfort was not referred to the region of the gallbladder. 3 Distention of the gallbladder did not produce vomiting. 4 It was not possible to reproduce the usual referred pain in the back, in the infrascapular region or in the right upper quadrant of the abdomen. 5 Distention of the gallbladder produced inspiratory distress. 6 When distention of the gallbladder brought that viscus into contact with the parietal peritoneum, localized pain was produced. 7 Two patients did not complain of discomfort, regardless of distention of the gallbladder.

Zollinger's observations indicate the following points: 1 Mechanical distention of the common duct produced epigastric distress which was more severe than that produced in the same patient by distention of the gallbladder. 2 Distention of the common duct produced vomiting in two of three patients. 3 There was no evidence of pain referred to the right upper quadrant of the abdomen or to the back. 4 Inspiratory distress was present. These observations have been confirmed by Carter,<sup>3</sup> who observed also that distention of the common duct frequently produced precordial pain.

Zollinger interprets his observations as indicating that true visceral pain is produced by distention of the gallbladder or common duct. Referred pain could not be produced in this manner and therefore is to be explained as due to the peritoneocutaneous radiation of Morley. This pain, he thinks, may well be of inflammatory origin.

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2 Zollinger, R., and Young, E. Observations on the Symptomatology of Cholelithiasis, with Special Reference to Vomiting, *New England J Med* **213** 714, 1935. Zollinger, R. Significance of Pain and Vomiting in Cholelithiasis, *J A M A* **105** 1647 (Nov 23) 1935.

3 Carter, R. F. Personal communication to the author.

An analysis of a series of cases of cholecystitis and cholelithiasis further confirmed the association of involuntary vomiting with stones in the common duct, and Zollinger therefore emphasizes the importance of this symptom as an indication for exploration of the common duct

#### THE RÔLE OF INFECTION IN CHOLECYSTITIS AND CHOLELITHIASIS

The pathogenesis of cholecystitis and cholelithiasis continues to arouse much controversy, though three factors—metabolic disturbance, infection and biliary stasis—are generally accepted as of prime importance in the development of these conditions and in the production of the associated symptoms. The relative importance of each of these factors is by no means established.

Early bacteriologic studies indicated that a great variety of organisms—especially typhoid and colon bacilli, streptococci, staphylococci and the Welch bacillus—could be isolated from cultures of material from the wall of the gallbladder, the bile or gallstones. The wall of the gallbladder showed changes that were interpreted as inflammatory, especially an infiltration with round cells. These changes were considered sufficient at that time to establish firmly the rôle of infection in producing chronic cholecystitis. Recent reviews, such as those of Andrews,<sup>4</sup> Rehfuess and Nelson,<sup>5</sup> Hanssen and Yurevich<sup>6</sup> and Andrews and Henry,<sup>7</sup> summarize most of the literature dealing with infection of the gallbladder. The authors point out that cultures of the bile or of tissue from different portions of the biliary tract are sterile in a considerable proportion of cases. Infection is more frequent in cases of acute cholecystitis than in cases of chronic cholecystitis. In the latter condition Hanssen and Yurevich obtained positive results from cultures of material from some portion of the biliary tract in only 32.7 per cent of the cases studied. The incidence of infection in the wall of the gallbladder (30 per cent) was greater than that in the contained bile (only 20 per cent).

Hanssen and Yurevich compared the results of culture of material obtained at duodenal drainage and of the contents of the gallbladder

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4 Andrews, E. Detailed Studies of a Series of Gall Bladder Cases, *Surg, Gynec & Obst* **57** 36, 1933

5 Rehfuess, M. E., and Nelson, G. M. The Problem of Infection in Gall Bladder Disease with a Report on the Experimental Production of Cholecystitis, *Am J Digest Dis & Nutrition* **1** 759, 1935, The Medical Treatment of Gall Bladder Disease, Philadelphia, W. B. Saunders Company, 1935

6 Hanssen, E. C., and Yurevich, A. Bacteriological Observations in Disease of the Biliary Tract. A Comparison of Operative Findings with Those of Non-Surgical Drainage of the Biliary Tract in One Hundred and Four Cases, *Am J Digest Dis & Nutrition* **2** 460, 1935

7 Andrews, E., and Henry, L. D. Bacteriology of Normal and Diseased Gallbladders, *Arch Int Med* **56** 1171 (Dec) 1935

obtained at operation. They point out that the relative infrequency with which infection of the bile is noted at operation contrasts markedly with the large proportion of positive results obtained from bile secured by duodenal drainage.

Some organisms, such as *Bacillus typhosus*, *Bacillus coli*, *Bacillus Welchii* and *Bacillus proteus*, normally are not found in the upper portion of the gastro-intestinal tract, but they do invade the biliary tract. When found in the duodenal drainage, they afford presumptive evidence of infection of the bile or biliary tract, irrespective of the presence of contaminating organisms.

Some organisms, such as the Friedlander bacillus, *Micrococcus catarrhalis*, pneumococci and the like, are normal inhabitants of the buccal cavity but are not found in cultures of material from the biliary tract at operation. When these organisms are found in the duodenal drainage, they afford presumptive evidence of duodenal contamination and are without pathologic significance.

The isolation of staphylococci and streptococci from the gallbladder at operation is significant. The presence of these organisms in the duodenal bile, however, is not significant of infection of the biliary tract, unless the possibility of contamination can be excluded, and even then these organisms must be obtained in pure culture on several occasions for the finding to be considered of clinical significance.

Recently, Twiss and Phillips<sup>8</sup> described a duodenal tube with a double bore. Duodenal drainage is carried out in the usual manner, one of the tubes being used for lavage of the duodenum with antiseptic solutions and to obtain specimens of bile for purposes of clinical study. The other tube is sealed off and kept sterile by means of a keratin-coated capsule over the duodenal opening. Once the tube is in position the capsule is ruptured, and specimens are withdrawn for culture. Twiss and Phillips have greatly reduced the incidence of contamination of the specimens of duodenal contents by securing the specimens in this manner, and the method promises to be of service in the study of infections of the biliary tract.

There has been a great deal of investigation in the past to determine the pathway by which infection reaches the liver and biliary tract. Three main pathways are recognized: (1) hematogenous, by way of either the portal vein or the hepatic artery, (2) chologenous, by way of an ascending infection of the bile ducts from the duodenum, and (3) lymphogenous, for lymphatic pathways carry infection to the liver and biliary tract from the appendix, duodenum and colon in particular.

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8 Twiss, J. R., and Phillips, C. H. Bacteriological Findings in Disease of the Biliary Tract. An Improved Method of Obtaining Cultures of Bile by Duodenal Drainage, *Am J Digest Dis & Nutrition* 2: 663, 1935.

They also carry infection from the liver to the gallbladder or vice versa. The relative importance of each of these pathways, however, continues to be a source of controversy.

Andrews<sup>9</sup> insists not only that the liver normally possesses a rich bacterial flora but that the demonstration of bacteria in the gallbladder is of no great significance unless the organisms are present in definitely increased amounts. Sections of the entire gallbladder show that the evidence of infection is greater in the cases in which there has been obstruction of the cystic duct. The pathologic changes, furthermore, often are more marked on the hepatic surface of the gallbladder than on the free surface. Andrews considers this as evidence that infection, when it occurs, spreads by direct continuity from the liver.

Andrews explains the relationship between infection and cholelithiasis on the assumption of the following premises: 1 Cholesterol stones are formed during short periods of obstruction of the cystic duct. During such periods bile salts are absorbed from the gallbladder, while cholesterol remains. The normal bile salt-cholesterol ratio is decreased, and cholesterol crystallizes. This cholesterol is derived from the bile and not from the epithelium of the gallbladder. 2 The deposition of calcium on a gallstone represents a secretion by the mucosa of the gallbladder during periods of obstruction. 3 The closure of the cystic duct due to any cause results in infection of the gallbladder, which lasts for a variable period. Calcium is not deposited during this period of infection but begins to accumulate as the infection subsides. 4 Infection of the gallbladder by hepatic bile is not likely. 5 Cholesterol stones are not the result of a diathesis, for they are not associated with hypercholesteremia, though a diathesis may be responsible for the deposition of pigment in cases of hemolytic jaundice.

Because he considers the patency of the cystic duct the crucial factor in determining the development of the pathologic picture, Andrews classifies his cases of gallbladder disease as follows:

1 Normal state of the gallbladder

Slight infiltration often seen, cholesterosis, presence or absence of stones  
(The presence of these signs formerly often led to a diagnosis of chronic cholecystitis)

2 Reaction to acute obstruction of the cystic duct

Uncomplicated type (formerly called chronic cholecystitis)

Infective type (formerly called acute cholecystitis)

Empyema (?)

Type with vascular damage (formerly acute cholecystitis)

Mild cholecystitis

Ulcerative cholecystitis

Gangrenous cholecystitis

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<sup>9</sup> Andrews, E. Pathologic Changes of Diseased Gallbladders. A New Classification, *Arch Surg* **31** 767 (Nov.) 1935



- 3 Reaction to intermittent obstruction of the common duct
  - Normal condition between attacks
  - Persistent irritation (usually mild)
- 4 Reaction to chronic obstruction of the cystic duct
  - Uncomplicated type (formerly called chronic cholecystitis)
  - Acute reinfection
    - Mild
    - Empyema (?)
  - Hydrops
- 5 Reaction to obstruction of the common duct
  - Acute or recent type (dilated and thin-walled gallbladder)
  - Chronic type (shrunken and fibrosed gallbladder)
- 6 Neoplasms

Many of the assumptions on which these views of Andrews are based are still subjects of controversy, and their truth is yet to be proved conclusively. The divergence between these views and those of Graham<sup>10</sup> are well-nigh irreconcilable. They should therefore provoke considerable discussion and further investigation of a very complicated and difficult subject.

Another approach to this problem was that of Carter,<sup>11</sup> who studied a series of cases of enlargement of the gallbladder consequent on stasis within the biliary tract. The condition was of two main types—hypotonic and hypertonic. The hypotonic type was ascribed to dilatation due to the normal secretory pressure of bile in the presence of atrophy and atony of the wall of the gallbladder. The gallbladder was rounded and balloon-like, but when stones became impacted and there was secondary infection, fibrosis and secondary contraction appeared. The hypertonic type also represented an enlargement due to an increase in the pressure within the biliary tract. In this type, however, the effects of the pressure were resisted by an increased tonus and hypertrophy of the wall of the gallbladder. Under these conditions the associated clinical symptoms were much more marked, and colic was frequent.

#### THE CHEMISTRY OF THE BILE ACIDS

Bile acids are the most characteristic constituent of bile, the secretion of the liver. Several different bile acids are known to exist in nature, and their chemical constitution has been under investigation for a long time, but in the past few years this field of chemistry has been revolutionized, and the structural formulas not only of the bile acids but of many chemically related compounds now are known. This sub-

10 Graham, E. A. Clinical Application of Some Recent Knowledge of Biliary Tract (Especially Cholesterosis or "Strawberry" Gall Bladder), Harvey Lectures, 1933-1934, Baltimore, Williams & Wilkins Company, 1935, p. 176.

11 Carter, R. F. Enlargement of the Gall Bladder, *Ann Surg* **102**: 194, 1935.

ject has recently been reviewed in detail by Sobotka<sup>12</sup> Reference must be made to his review for details, for Sobotka reports that over five hundred compounds chemically related to the bile acids have been described and he cites over three hundred references in his bibliography

The bile acids are derivations of the polycyclic hydrocarbon cholane which is related to the phenanthrene compounds Interest in these compounds is heightened by the recognition that many other compounds of great biologic and medical interest have this same tetracyclic carbon skeleton Thus, the bile acids of both the cholic and the deoxycholic series and their derivatives, the various sterols, such as cholesterol, phytosterol, ergosterol and vitamin D, the aglucone group of various glucosides, such as saponin, strophanthin and some of the toad poisons, some hormones, including the ovarian and testis hormones as well as the hormone of the corpus luteum, and certain carcinogenic substances prepared synthetically or isolated from coal tar are all related chemically (figure)

The physiologic or pharmacologic action of many of these compounds has been studied in detail, but biochemical knowledge is lacking At present the natural synthesis of these compounds in the body and the manner and method of their catabolism are unknown There has been much speculation in consequence regarding their biochemical relationships, if any Are they mutually interconvertible, if so, which ones? Particularly fascinating is the suggestion that a disturbance in or a perversion of the normal catabolism of bile acids or of cholesterol might lead to the formation in significant amounts of carcinogenic compounds, but it must be kept in mind that until more is known of the metabolism of these compounds there is no direct evidence to support such a hypothesis

The physiologic action of the bile acids is better understood It has been shown that in an animal with a biliary fistula the daily excretion of bile acids or salts depends on the diet<sup>13</sup> When bile salts are administered, either orally or intravenously, they are rapidly excreted through the bile<sup>14</sup> A reduction in the excretion of bile salts is one of the earliest signs of injury to the liver by such a hepatic poison as chloroform<sup>15</sup> When the bile ducts are obstructed, bile salts accumulate in the blood

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12 Sobotka, H The Chemistry of the Bile Acids and Related Substances, *Chem Rev* **15** 311, 1934

13 Smith, H P, and Whipple, G H Bile Salt Metabolism V Casein, Egg Albumin, Egg Yolk, Blood and Meat Proteins as Diet Factors, *J Biol Chem* **87** 689, 1930

14 Greene, C H, and Snell, A M Studies in the Metabolism of the Bile II The Sequence of Changes in the Blood and Bile Following the Intravenous Injection of Bile or Its Constituents, *J Biol Chem* **78** 691, 1928

15 Smith, H P, and Whipple, G H Bile Salt Metabolism VIII Liver Injury and Liver Stimulation, *J Biol Chem* **89** 727, 1930

stream and are excreted in the urine<sup>16</sup> As a result of these experiments it is generally accepted that the bile acids are formed in the liver Further evidence in support of this view is supplied by the observation of Greene<sup>17</sup> and of Bollman and Mann<sup>18</sup> that bile salts do not appear in the blood or urine after complete hepatectomy

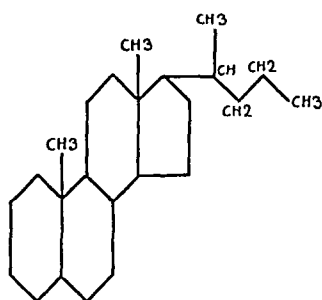
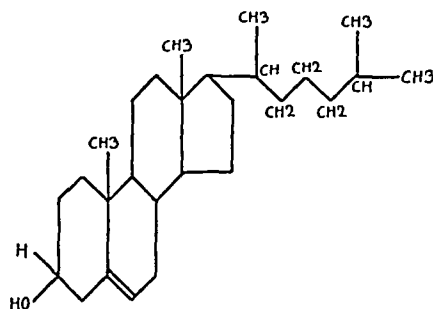
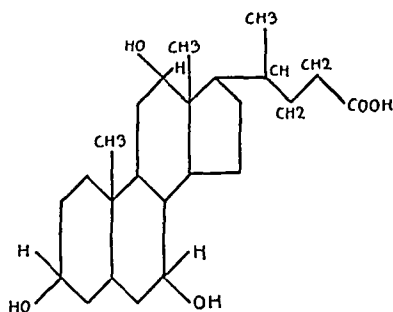
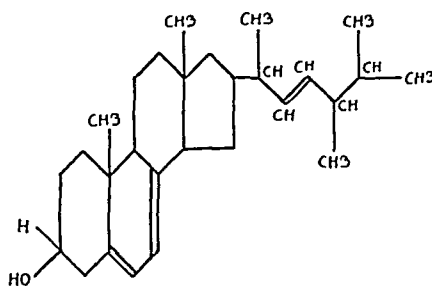
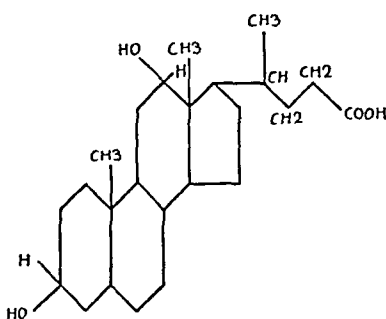
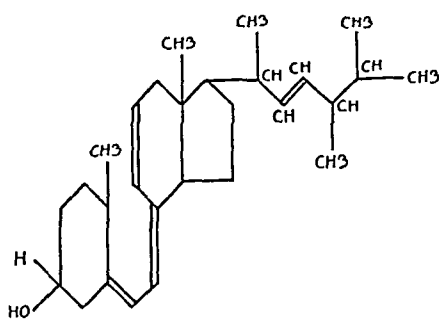
*Cholane**Cholesterol**Cholic Acid**Ergosterol**Deoxycholic Acid**Tachysterol (Vitamin D<sup>2</sup>)*

Fig 1—Formulas for cholane and related compounds (modified from Sobotka)

16 Snell, A M , Greene, C H , and Rowntree, L G Diseases of the Liver VII Further Studies in Experimental Obstructive Jaundice, Arch Int Med **40** 471 (Oct ) 1927

17 Greene, C H Unpublished observation

18 Bollman, J L, and Mann, F C The Influence of the Liver on the Destruction of Bile Salt, Arch Path **16** 304 (Aug ) 1933, Alterations in Hepatic Function Produced by Experimental Hepatic Lesions, Ann Int Med **9** 617, 1935

The importance of bile in the absorption of fats has long been known and is partly due to its action in activating the pancreatic lipase and partly to the action of the bile salts in favoring emulsification and

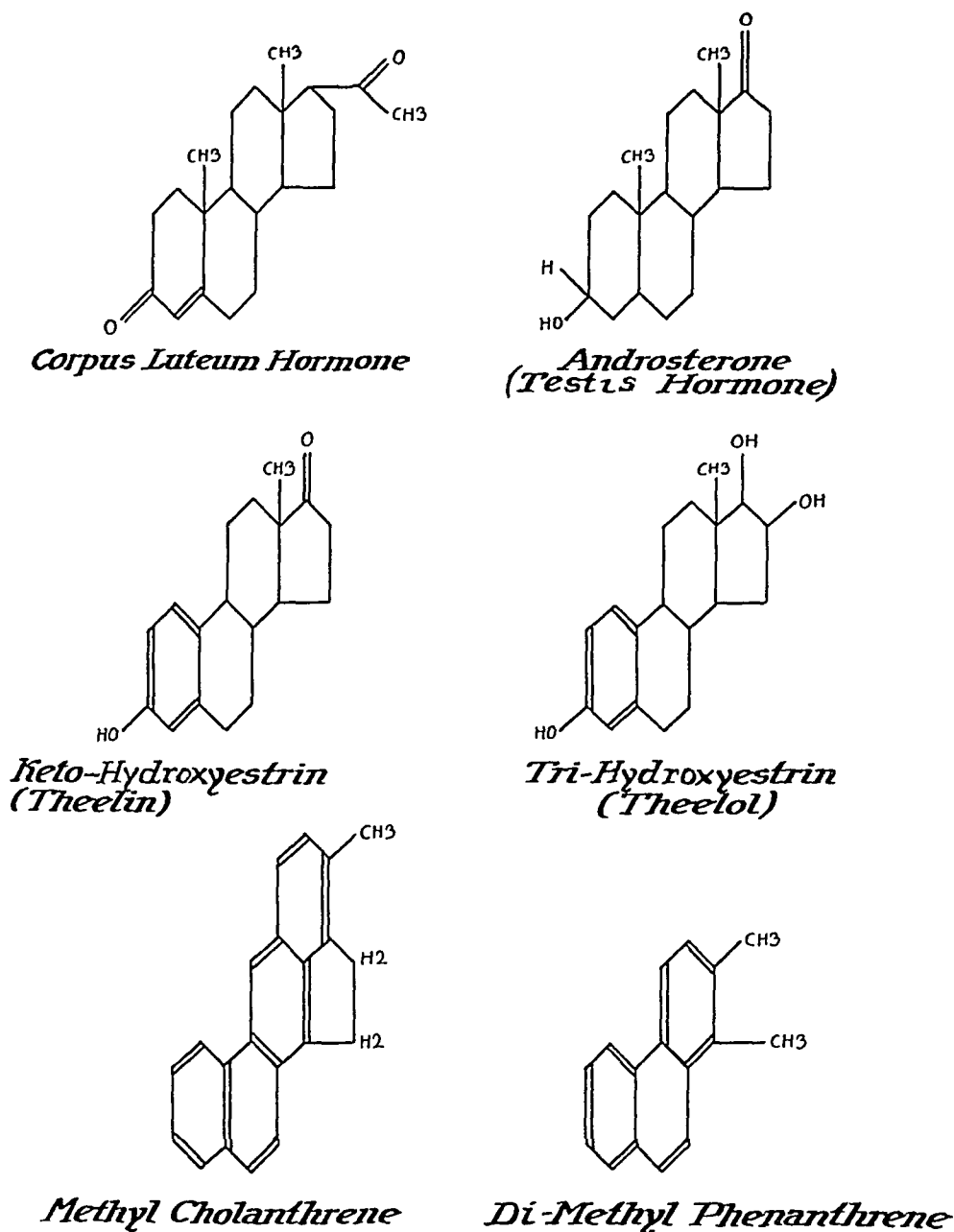


Fig 2—Formulas for cholane and related compounds (continued)

solution of the fats Wieland and Sorge<sup>19</sup> showed that the so-called choleic acids in bile really are addition compounds of deoxycholic acid

<sup>19</sup> Wieland, H, and Sorge, H Untersuchungen über die Gallensauren zur Kenntnis der Choleinsäure, Ztschr f physiol Chem **97** 1, 1916

with fatty acids Verzar and Kuthy<sup>20</sup> have emphasized the importance of such compounds in the absorption and transport of fatty acids, for they are water-soluble and may be absorbed directly into the portal circulation Drummond<sup>21</sup> adds further emphasis by stating that "the most important function of the bile is to facilitate the absorption of fatty substances by the formation of these curious complexes with bile acids"

It is clear that the property of the bile acids in favoring the absorption of fatty substances is not limited to the true fats but is extended to a large series of "fat-soluble" materials Drummond cites experiments showing the absorption of such unrelated compounds as liquid petrolatum and naphthalene

The practical importance of this aspect of the absorption of "fat-soluble" materials is apparent when the vitamins are considered Wright and Whipple<sup>22</sup> reinvestigated the absorption of cholesterol after oral administration to dogs and showed that the excretion through the biliary fistula is increased by the feeding of bile or bile salts with the cholesterol Greaves and Schmidt<sup>23</sup> have shown that in rats the absorption of vitamin D is deficient when bile is excluded from the intestinal tract

Greaves and Schmidt<sup>24</sup> placed rats on a diet deficient in vitamin A and then excluded bile from the intestinal tract either by ligation of the common bile duct or by the production of a biliary fistula Tests showed that these animals were able to absorb vitamin A in the absence of bile from the intestinal tract The carotenes ( $\alpha$ ,  $\beta$  and  $\gamma$ ) are now recognized as being the precursors of vitamin A and are frequently referred to as the provitamin Carotene administered orally was not absorbed when bile was excluded from the intestinal tract Carotene forms addition compounds with deoxycholic acid and was absorbed when administered along with deoxycholic acids Animals with experimental obstructive jaundice produced by ligation of the common duct were unable to convert carotene into vitamin A, irrespective of the

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20 Verzar, F, and von Kuthy, A Die Bedeutung der Gallensauren fur die Fettresorption, *Biochem Ztschr* **205** 369, 1929, Die Bedeutung der gepaarten Gallensauren fur die Fettresorption, *ibid* **230** 451, 1931 Verzar, F Absorption of Fats, *Nutrition Abstr & Rev* **2** 441, 1933

21 Drummond, J C Biochemical Studies of Liver Function in Relation to Fat Metabolism, *Harvey Lectures, 1932-1933*, Baltimore, Williams & Wilkins Company, 1934, p 202

22 Wright, A, and Whipple, G H Bile Cholesterol Fluctuations Due to Diet Factors, Bile Salt, Liver Injury and Hemolysis, *J Exper Med* **59** 411, 1934

23 Greaves, J A, and Schmidt, C L A The Role Played by Bile in the Absorption of Vitamin D in the Rat, *J Biol Chem* **102** 101, 1933

24 Greaves, J D, and Schmidt, C L A On the Absorption and Utilization of Carotene and Vitamin A in Choledochocolonostomized Vitamin A Deficient Rats, *Am J Physiol* **111** 492, 1935, The Utilization of Carotene by Jaundiced and Phosphorus Treated Vitamin A Deficient Rats, *ibid* **111** 502, 1935

channel used in giving the carotene. These experiments therefore tend to strengthen the present view that the liver is the organ responsible for the conversion of carotene to vitamin A. Does this indicate that the marked degree of carotenemia which is occasionally seen in clinical practice is evidence of disturbance of this function of the liver?

Clinicians have long recognized the variety and severity of the nutritional disturbances seen in cases of obstructive jaundice. That some of these symptoms may be produced by a deficiency of vitamin A has not been recognized so clearly. Altschule<sup>25</sup> reports a postmortem study of eleven infants with congenital atresia of the bile ducts. All the infants had received a diet that contained adequate amounts of vitamin A, and none presented evidence of xerosis or keratomalacia during life. In more than half the cases Altschule observed histologic evidence of a deficiency of vitamin A. This is a significant observation, and it is to be hoped that the study will be extended to cases of obstructive jaundice in adults.

#### CIRRHOSIS OF THE LIVER

In the previous review<sup>1</sup> it was pointed out that the term "hepatic cirrhosis" is synonymous with "chronic diffuse hepatitis." The etiology of the term is as varied as are the agents which, singly or in combination, may cause chronic diffuse progressive injury to the liver. Arsenic and its derivatives have been under suspicion for a considerable period as agents which may produce hepatic lesions. This suspicion is further increased by the studies of Baldrige,<sup>26</sup> who reviewed a series of thirty-six selected cases in which the diagnosis of portal cirrhosis was unquestioned. Of the thirty-six patients, fifteen had syphilis, and eleven of these patients had received antisyphilitic treatment before cirrhosis became manifest. One additional patient was not syphilitic but had received antisyphilitic treatment.

Baldrige agrees that vices are prone to be multiple, so that alcoholism, syphilis and antisyphilitic treatment often coexist in the history of a patient with cirrhosis of the liver, but he points out that alcoholism apparently was an etiologic agent in only three of the twelve cases reported.

In seven of the cases the Wassermann reaction was negative when cirrhosis developed, and in only two was the reaction strongly positive. The facts that most of the patients had had vigorous treatment and that cirrhosis had developed at a time when the Wassermann reaction was negative speaks against the theory that the hepatic damage was dependent

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25 Altschule, M. D. Vitamin A Deficiency in Spite of Adequate Diet in Congenital Atresia of Bile Ducts and Jaundice, *Arch. Path.* **20** 845 (Dec.) 1935.

26 Baldrige, C. W. The Relationship Between Antisyphilitic Treatment and Toxic Cirrhosis, *Am. J. M. Sc.* **188** 685, 1934.

on the syphilitic infection. The fact that there was a variable duration of syphilis before cirrhosis appeared and the fact that one patient never had syphilis are opposed to the theory that the cirrhosis in these patients may have been due to syphilis.

In three of the four cases in which necropsy was performed cirrhosis was described by the pathologist as being toxic, the result of previous acute yellow atrophy. As a result of these observations Baldrige believes that toxic cirrhosis of the liver may and does result from anti-syphilitic treatment.

#### TESTS OF HEPATIC FUNCTION

No attempt will be made here to review the various reports on tests of hepatic function, for a detailed review of the current tests and an estimate of their clinical usefulness are given by Soffer.<sup>27</sup> Of the various tests which are making a bid for recognition, reference may be made to the study of the synthesis of hippuric acid from ingested benzoic acid as a test of hepatic function, for this well illustrates the difficulties in the development of really specific functional tests. This test was introduced by Kuhne<sup>28</sup> in 1858, was gradually given up, then was reintroduced as a measure of renal rather than of hepatic injury and finally was reintroduced as a test of hepatic function by Quick<sup>29</sup> in 1933. Vaccaro<sup>30</sup> and Snell and Plunkett<sup>31</sup> have reported several cases showing that the synthesis of hippuric acid is diminished in the various types of hepatic disease. They believe, therefore, that the test is of value in the search for evidence of hepatic damage in patients with "surgical" types of jaundice.

Adlersberg and Minibeck<sup>32</sup> confirm these findings but in addition report that the synthesis of hippuric acid decreases in nephritis and in a variety of other conditions, such as chronic passive congestion, anemia and cachectic states. They think that disturbance in the absorption of the administered benzoic acid may explain the diminished synthesis of

27 Soffer, L. J. Present Day Status of Liver Function Tests, *Medicine* **14** 185, 1935.

28 Kuhne, W. Beitrage zur Lehre vom Icterus. Eine physiologisch-chemische Untersuchung, *Virchows Arch f path Anat* **14** 318, 1858.

29 Quick, A. J. Synthesis of Hippuric Acid. A New Test of Liver Function, *Am J M Sc* **185** 630, 1933.

30 Vaccaro, P. F. The Synthesis of Hippuric Acid. Its Value in Detecting Hepatic Damage Secondary to Diseases of the Extrahepatic Biliary System, *Surg, Gynec & Obst* **61** 36, 1935.

31 Snell, A. M., and Plunkett, J. E. The Hippuric Acid Test for Hepatic Function. Its Relation to Other Tests in General Use, *Am J Digest Dis & Nutrition* **2** 716, 1936.

32 Adlersberg, D., and Minibeck. Ist die Hippursäureausscheidung nach Belastung mit Benzoesäure eine brauchbare Leberfunktionsprüfung? *Ztschr f klin Med* **129** 392, 1936.

hippuric acid in the latter conditions. That severe injury to the liver interferes markedly with the synthesis and excretion of hippuric acid is agreed, but it must be recognized that the liver is not the only organ concerned in the metabolism of hippuric acid. Disturbances in the absorption from the intestine or in renal function likewise reduce the excretion of hippuric acid. The test is useful in the study of hepatic disease, but other disturbing factors must be excluded, and the test should not be considered as specific for hepatic function.

The generally accepted view regarding the use of tests of hepatic function still is that it is desirable to test as many different functions of the liver as possible in order satisfactorily to appraise the functional status of this organ. A good deal of the present dissatisfaction with these tests is due to the tendency to rely on one particular test. Particularly is this true of the tendency to search for tests which will indicate the specific pathologic lesion in the liver. There is no correlation between the type of pathologic lesion and the function which is disturbed. Clinical signs likewise fail to indicate which function is disturbed first. Functional tests have not reached the point of perfection where the nature of the test can indicate the type of change in the organ. As pointed out by Greene and Shattuck,<sup>33</sup> continuance of the search for functional tests of specific diagnostic import is not likely to be successful, rather, the tests should be used in an attempt to determine the importance of the various elements which enter into the clinical picture.

#### EFFECTS OF HEPATIC DISEASE ON THE COMPOSITION OF THE BLOOD

The changes in the serum proteins in diseases of the liver were referred to in part in the previous review. During the year this subject has been reviewed in detail by Snell,<sup>34</sup> with particular reference to the changes in the serum proteins. He refers to a long series of reports demonstrating that in the more advanced stages of chronic hepatic disease there is a moderate reduction in the serum protein content. The albumin-globulin ratio of the serum also is disturbed, with a tendency to a disproportionate lowering of the albumin content, and a reversal of the normal albumin-globulin ratio. These variations may be nutritional or secondary to a loss of protein in ascetic or edema fluid, but the preponderance of evidence seems to indicate that the changes are associated with a deficient production of protein by the liver, and so

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<sup>33</sup> Greene, C. H., and Shattuck, H. F. The Clinical Use of Tests of Hepatic Function, *Am J Digest Dis & Nutrition* **1** 505, 1931.

<sup>34</sup> Snell, A. M. The Effects of Chronic Disease of the Liver on the Composition and Physicochemical Properties of Blood. Changes in the Serum Proteins, Reduction in the Oxygen Saturation of the Arterial Blood, *Ann Int Med* **9** 690, 1935.



they have some diagnostic and prognostic significance. The reduction in the serum albumin value frequently is sufficient so that it is a contributing factor in the production of ascites and edema.

The Takata-Ara reaction continues to gain in favor as a measure of the disturbances in the normal albumin-globulin ratio of the serum and so as an index of parenchymatous lesions of the liver. Rappolt,<sup>35</sup> Ragins<sup>36</sup> and Recht<sup>37</sup> all consider it of distinct clinical value. The experiments of Oefelein<sup>38</sup> concerning the mechanism of the Takata-Ara reaction indicate that the outcome of the test was determined by the ammonia present. In his patients he found a parallelism between the Takata-Ara reaction and the ammonia content of the serum. He therefore questions the usually accepted explanation of the mechanism of the test, but since an increase in the ammonia content of the serum is evidence of failure in the detoxifying mechanism of the liver, he too considers a positive reaction as evidence of parenchymal lesions of the liver. Gros<sup>39</sup> takes the opposite view, for he obtained a positive Takata-Ara reaction in the serum of patients with multiple myeloma. This reaction in cases of myeloma is explained as due to the disturbances in the character of the serum proteins in this condition and so emphasizes the point that the Takata-Ara reaction is not specific for hepatic lesions. This is also stressed by Magath,<sup>40</sup> who points out that the Takata-Ara reaction is a colloidal phenomenon which has not yet been explained. Its use in diagnosis is therefore empirical, though there is some correlation with changes in the albumin-globulin ratio of the serum. Magath found a positive reaction in about half his patients with hepatic damage, and so he questions whether the test is of greater diagnostic or prognostic value than other established tests of hepatic function, such as the bromsulfalein test. I likewise have been disappointed in the results of the Takata-Ara reaction, for in many cases there are slight flocculations or precipitations which are very difficult of interpretation, and the results in known cases of hepatic involvement have not been uniformly positive.

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35 Rappolt, L. Modified Takata Reaction in Liver Disease, *Munchen med Wchnschr* **82** 243, 1935

36 Ragins, A. B. Value of Takata and Ara Reaction as Diagnostic and Prognostic Aid in Cirrhosis of Liver, *J Lab & Clin Med* **20** 895, 1935

37 Recht, S. Hepatic Function and Significance of Takata Reaction in Disorders of Nurslings and of Small Children, *Ztschr f Kinderh* **57** 383, 1935

38 Oefelein, F. Mechanism of Takata-Ara Reaction and Its Practical Significance as Functional Test of Liver, *Klin Wchnschr* **14** 56, 1935

39 Gros, W. Problem of Regular Changes of Blood Protein in Multiple Myeloma. Significance of Blood Protein Bodies for Takata's Reaction in Blood, *Deutsches Arch f klin Med* **177** 461, 1935

40 Magath, T. B. The Takata-Ara Test of Liver Function, *Am J Digest Dis & Nutrition* **2** 713, 1936

The disturbances in the process of blood formation in hepatic disease are not limited to the plasma, for there are changes in the cellular elements as well. Anemia is frequently associated with hepatic diseases, and Hayem<sup>41</sup> in 1889 reported a case of cirrhosis in which the blood picture resembled that seen in pernicious anemia. The increased interest in pernicious anemia stimulated by the discovery of the specific therapeutic effects of liver extracts has extended to other conditions in which similar blood pictures are seen. As a result, during the last few years a considerable number of reports have been made on the occurrence of macrocytic hyperchromic anemia in association with diseases of the liver, especially in cases of portal cirrhosis.<sup>42</sup> These studies have been reviewed by Wintrobe,<sup>43</sup> who reported a study of one hundred and thirty-two cases of hepatic disorder. Eighteen (40.9 per cent) of the forty-four patients with hepatic cirrhosis, eight (22 per cent) of the thirty-six patients with carcinoma of the liver, either primary or secondary, and seventeen (32.7 per cent) of the fifty-two patients with miscellaneous disorders of the liver showed a macrocytic anemia morphologically similar if not identical with that seen in pernicious anemia. Like the latter it manifested spontaneous remissions and responded to treatment with liver extract.

Hepatic disease is apparently the cause of this macrocytic anemia, for the latter was most marked in those cases in which the disease of the liver was so widespread and of such long duration that only a little functioning tissue remained. This is particularly true in cases of hepatic cirrhosis, in which condition macrocytic anemia is especially common. Faulty storage of the hematopoietic principle in the cirrhotic liver has

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41 Hayem, G. *Du sang et ses alterations anatomiques*, Paris, G. Masson, 1889, p. 932.

42 Schulten, H., and Malamos, B. *Ueber Veränderungen der roten Blutkörperchen bei Lebererkrankungen*, *Klin Wchnschr* **11** 1338, 1932. Gamna, C. *Ueber Veränderungen der roten Blutkörperchen bei Lebererkrankungen*, *ibid* **12** 348, 1933. Fellingner, K., and Klima, R. *Untersuchungen über Anämien bei Leberzirrhosen*, *Wien klin Wchnschr* **46** 1191, 1933. Wintrobe, M. M., and Shumaker, H. B. *The Occurrence of Macrocytic Anemia in Association with Disorders of the Liver*, *Bull Johns Hopkins Hosp* **52** 387, 1933. Cheney, G. *The Morphology of Erythrocytes in Cirrhosis and Other Disorders of the Liver*, *California & West Med* **39** 90, 1933. Van Duyn, J., Jr. *Macrocytic Anemia in Disease of the Liver*, *Arch Int Med* **52** 839 (Dec.) 1933. Goldhamer, S. M. *Liver Extract Therapy in Cirrhosis of the Liver*, *ibid* **53** 54 (Jan.) 1934. Kordenat, R. A. *The Relation of Anemia to Surgical Diseases of the Gall Bladder*, *Am J Digest Dis & Nutrition* **1** 638, 1934. Wright, D. O. *Macrocytic Anemia and Hepatic Cirrhosis*, *Am J M Sc* **189** 115, 1935.

43 Wintrobe, M. M. *Relation of Disease of the Liver to Anemia. Type of Anemia, Response to Treatment, and Relation of Type of Anemia to Histopathologic Changes in Liver, Spleen and Bone Marrow*, *Arch Int Med* **57** 289 (Feb.) 1936.

been suggested as the cause of the anemia. It is known that this principle is stored in the normal liver, while the reports of Robscheit-Robbins and Whipple,<sup>44</sup> Wilkinson and Klein<sup>45</sup> and Goldhamer, Isaacs and Sturgis<sup>46</sup> have shown that extracts of the liver of a patient who had died of cirrhosis and macrocytic anemia were ineffective in the treatment of a patient with pernicious anemia. An extract of the liver of a patient who had died of acute yellow atrophy contained the active hematopoietic principle.

Previous authors have suggested that in cases of cirrhosis the liver may be unable to utilize the hematopoietic principle, but Wintrobe insists that there is no evidence to indicate that in cases of hepatic disease there is any difficulty in utilizing the extrinsic factor from the diet or that the liver has any other function concerning this factor than that of simple storage. He thinks that the ability of the patient to utilize the extrinsic factor may explain why macrocytic anemia is rarely severe in cases of hepatic disease.

Not only do the anemia and the consequent reduction in the hemoglobin content of the blood in cases of advanced hepatic disease have an unfavorable effect on the course of the disease, but in these cases the hemoglobin fails to carry its full load of oxygen. Snell<sup>34</sup> has reported the existence of a considerable degree of anoxemia in patients with advanced hepatic disease of various types. In these cases the percentage of saturation of the arterial blood observed varied from 85 to 90, instead of showing the normal range of from 91 to 98. His results showed that the anoxemia was of the anoxic type, and he was unable to demonstrate any changes in the physiologic behavior of the hemoglobin to explain this finding. Circulatory disturbances and minor degrees of edema of the alveolar walls cannot be excluded in the production of this condition, though Snell minimizes the importance of these factors. In any case the anoxemia, when present, can have only a deleterious effect on the clinical condition of the patient. These observations led Judd, Snell and Hoerner<sup>47</sup> to reemphasize further the beneficial effects of transfusion, especially in the preoperative preparation of jaundiced patients.

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44 Robscheit-Robbins, F. S., and Whipple, G. H. Hemoglobin Production Factors in the Human Liver. II. Liver Degeneration, Cancer, Cirrhosis and Hepatic Insufficiency, *J. Exper. Med.* **57**: 653, 1933.

45 Wilkinson, J. F., and Klein, L. The Haemopoietic Activity of the Normal and Abnormal Human Liver, *Quart. J. Med.* **3**: 341, 1934.

46 Goldhamer, S. M., Isaacs, R., and Sturgis, C. C. The Role of the Liver in Hematopoiesis, *Am. J. M. Sc.* **188**: 193, 1934.

47 Judd, E. S., Snell, A. M., and Hoerner, M. T. Transfusion for Jaundiced Patients, *J. A. M. A.* **105**: 1653 (Nov. 23) 1935.

## Book Reviews

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**The Stomach and Duodenum** By George B Eusterman, M D , Donald G Balfour, M D , and members of the staff of the Mayo Clinic Price, \$10 Pp 958, with 436 illustrations Philadelphia W B Saunders Company, 1935

For many years the staff of the Mayo Clinic has taken a notable interest in conditions which affect the stomach and duodenum George Eusterman and Donald Balfour are physicians of wide experience in these matters, they have a sound clinical opinion on any subjects which happen to interest them and a pungent way of expressing this and are likely to do any job which they undertake artistically and in a thorough, painstaking fashion It is not surprising, therefore, that this volume which has been assembled under their leadership is an admirable bit of bookmanship

The work begins with a characteristic foreword by Dr William Mayo and Dr Charles Mayo, who so long and emphatically have championed progressive medicine The following chapters deal with various topics that pertain to the stomach or duodenum, the discussion is based largely on the experience of the Mayo Clinic, with due regard to the current literature and to the opinions of others These chapters are written authoritatively and interestingly by either Dr Eusterman or Dr Balfour except when outside help seemed necessary Thus, while the brunt of the writing of this long book has fallen on their shoulders, there are a number of extremely valuable chapters by other members of the staff Alvarez writes on physiology, and Mann, on experimental peptic ulcer MacCarty and Robertson contribute a section on pathology Kirklin discusses the roentgenologic diagnosis and Lundy discusses anesthesia for gastric operations, while Walters writes on total gastrectomy for carcinoma of the stomach, Harrington, on diaphragmatic hernia, Helmholz, on hypertrophic pyloric stenosis of infants, Rivers, on gastric or duodenal hemorrhages, Hartman, on anemia following operation on the stomach, and Lemon, on postoperative pulmonary disease The first chapter, by Dwight Wilbur, gives in twenty-one pages an excellent historical review of the steps by which the present conception of diseases of the stomach and duodenum have arisen

A book of this scope and character is bound to be a useful work for reference Moreover, it is well printed, well illustrated and well bound It will appeal to students and teachers, and to those practicing clinicians who are doing the field work of medicine today in this country, for whom it was written On the whole, this work deserves the highest praise

**Pathology of Internal Diseases** By William Boyd, M D , Professor of Pathology in the University of Manitoba Second edition Price, \$10 Pp 904, with 335 illustrations Philadelphia Lea & Febiger, 1935

This book had a successful coming out in 1931 Such critical dowagers as *The Journal of the American Medical Association* and the ARCHIVES OF INTERNAL MEDICINE were disposed to look favorably on the form and appurtenances of this new debutante To be sure, *The Journal* as an elderly matron always responsible for the proper thing to say, raised eyebrows at some of the English used by the new book, objecting particularly to the tediousness of repeated beginnings such as "It is seen that", "It appears", and "It becomes evident," and shuddering at "In one case on which I performed an autopsy" (p 698) and the "case which was tapped 301 times" (p 331) On the whole, however, both critics were pleased *The Journal of the American Medical Association* (96 973 [March 21] 1931) concluded by remarking, "The author is to be congratulated on his success in linking up the pathology so commonly segregated to instructors and student days with the routine practice of medicine," and the ARCHIVES OF INTERNAL MEDICINE (47 988

[June] 1931) stated "No text in the field of internal medicine that has appeared in recent years deserves more praise. It is different, readable, valuable as a reference book and in every way written from the point of view of the clinical teacher and practitioner."

The second edition is much like the first but is ninety-three pages longer and has thirty-five more illustrations. There still remain a tediously large group of sentences which begin "It is seen that", "It appears," and "It becomes evident," and on pages 719 and 337 one still reads of the "case on which I performed an autopsy" and of the "case on record which was tapped 301 times." But these, after all, are minor defects. As the author states, to this edition much new material has been added and a considerable amount has been rewritten, so that the book is distinctly up to date in every way. A pleasant improvement is in the manner in which the short bibliography at the end of each chapter is arranged. In the first edition this was set down in alphabetical order, in the new edition the bibliography is arranged first by subjects and then alphabetically, so that the student can more easily lay his hand on good references to any subject on which he wishes more detailed knowledge.

The author is to be congratulated. In his second edition he has continued to make of his book an interesting, useful, first-class volume on pathology. The ARCHIVES, at least, is glad to repeat, "No textbook in the field of internal medicine that has appeared in recent years deserves more praise!"

### **The Human Foot Its Evolution, Physiology and Functional Disorders**

By Dudley J. Morton, Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Price, \$3. Pp 257, with 100 illustrations. New York: Columbia University Press, 1935.

Eminently fitted for the task by his years of painstaking study of the foot, as both clinician and anatomist, Morton brings together in this volume a compact and stimulating discussion which aims chiefly "to identify and to analyse the primary factors of functional disorders of the foot."

More than half of the book is devoted to anatomic and functional considerations, which are properly emphasized as an indispensable foundation for the understanding of disorders of the foot. Tracing the evolutionary history of the human foot, the author states that it derives remotely from a grasping member "as flexible and as flat as the human hand," adapted to the demands of a tree-living existence. The elevation of a rigid longitudinal arch is explained as a response to the assumption of erect bipedal locomotion by the more immediate ancestors of modern man, introducing new gravitational stresses and changes in muscle pull, both being mechanical influences capable of modeling the skeletal pattern. Formation of the arch and the new distributions of stresses are associated with further modifications of foot structure, involving notably the calcaneus and talus. Distribution of weight and the axis of balance in standing, foot balance, and the foot in action, in both walking and running stride—all are analyzed in detail. Contrary to those who affirm either that the maintenance of normal posture is brought about entirely by the action of muscles or that normal posture depends essentially on the ligamentary supports, Morton insists that "any appreciable defect in either element will be manifested by an unbalanced posture, irrespective of the integrity of the other element."

In the detection of foot disorders the author finds that while degree of pronation reveals disorders of the longitudinal arch, mere surface inspection affords little help in identifying present or prospective disorders in the distal part of the foot. He accordingly adopts, in addition to roentgen examination a physiologic test, having devised for this purpose two instruments for recording distribution of weight in standing and in walking. The results for one hundred and fifty subjects so analyzed are presented in detail, and attention is directed to the desirability of routine roentgenography in the diagnosis of functional disorders. In a concluding chapter, devoted to the general problem of foot welfare, it is stated that examinations of male college students indicate that as many as 40 per cent exhibit foot disorders sufficient to produce symptoms or even to limit normal activity. It is

obvious that most cases of this nature would not come to the attention of the orthopedist, and being sought in extraprofessional quarters

**Preventive Medicine and Hygiene** By Milton J Rosenau, Professor of Preventive Medicine and Hygiene, Harvard University Medical School With chapters on Mental Hygiene, by Abraham Myerson, Sewage and Garbage, by Gordon M Fair, Vital Statistics, by John W Trask, Statistical Methods, by Carl P Doering, Conservation of Vision, by J Herbert Waite, Contraception, by Eric M Matsner Sixth edition Price, \$10 Pp 1,481, with 146 illustrations and 1 plate New York D Appleton-Century Company, Inc, 1935

The first edition of this textbook appeared in 1913 It was reviewed favorably in *The Journal of the American Medical Association* (61 1317 [Oct 4] 1913) The reviewer described the book as a distinct addition to the lengthening list of books of the first rank by American authors and already a standard authority on the subject of preventive medicine

The book has prospered Subsequent editions were forthcoming in 1916, 1917, 1921, 1927 and 1935 The latest edition, while in line with the others, has been extensively rewritten to bring it up to date, with much new matter added and much dead wood deleted Subjects considered for the first time include contraception and psittacosis, which have become of considerable general importance in the last few years The review of the fifth edition in *The Journal of the American Medical Association* (88 1924 [June 11] 1927) stated about all that needs to be said in regard to the 1935 volume "This book established itself as a standard in its field when first published, and succeeding editions have been quite up to the rank of the previous ones In every way the volume is an adequate reference to its subject"

**The Parathyroids in Health and in Disease** By David H Shelling, M D Price, \$5 Pp 335, with 26 illustrations St Louis C V Mosby Company, 1935

This is an admirable book As Shelling states in the preface, the parathyroids recently have attracted a great deal of general interest The physiologists, chemists, pathologists and even the clinicians have made definite contributions to the knowledge of the parathyroids, all within a few years The aim of this monograph is to bring together all this knowledge in a manner that both the investigator and the clinician will find palatable

The book is well planned First there is an excellent chapter on history, then come three chapters dealing with the anatomy, pathology and physiology of the parathyroids These are followed by a section dealing with the parathyroid hormone and finally by chapters on hypoparathyroidism, hyperparathyroidism, the relation of the parathyroids to other glands of internal secretion and the clinical use and misuse of parathyroid hormone and of parathyroidectomy Each chapter is accompanied by a good list of references to the subject under consideration As an appendix are detailed typical diets low in calcium and phosphorus that have been utilized by clinical investigators who have studied calcium and phosphorus metabolism

On the whole, this is a useful reference book It appears to fulfil adequately the purpose for which it was written It will prove valuable to any one in the least interested in the parathyroid glands The author deserves great praise for assembling and correlating in such a scholarly and interesting fashion so wide a range of material

**The Harvey Lectures** Delivered Under the Auspices of the Harvey Society of New York, 1933-1934 Series 29 Price, \$4 Pp 262 Baltimore Williams & Wilkins Company, 1935

This volume of the Harvey Society of New York begins with the obituary account, from the minutes of the society, of the life and work of its president,

Dr Alfred Fabian Hess Dr Hess died while holding this office The volume contains the following Harvey lectures

"Typhus and Rocky Mountain Spotted Fever in the United States," by Dr R E Dyer, Surgeon, National Institute of Health

"The Potential Energies of Oxidation-Reduction Systems and Their Biochemical Significance," by Dr W Mansfield Clark, Professor of Physiological Chemistry, Johns Hopkins School of Medicine

"Heteroplastic Grafting in Embryology," by Dr Ross G Harrison, Sterling Professor of Biology, Yale University

"The Estrogenic Substances," by Dr E A Doisy, Professor of Biological Chemistry, St Louis University School of Medicine

"The Clinical Application of Some Recent Knowledge of the Biliary Tract and of the Pancreas," by Dr Evarts A Graham, Professor of Surgery, Washington University School of Medicine, St Louis

"The Significance of Morbid Processes in the Fetus," by Dr George L Streeter, Director, Department of Embryology, Carnegie Institution of Washington, Baltimore

"Filtrable Viruses with Particular Reference to Psittacosis," by Dr Thomas M Rivers, Member of the Rockefeller Institute, New York

"The Nervous Mechanism of Cardio-Vascular Control," by Dr Detlev W Bronk, Johnson Professor of Biophysics, University of Pennsylvania

**The Autonomic Diseases or the Rheumatic Syndrome** By T M Rivers, M D Price, \$3 Pp 299 Philadelphia Dorrance & Company, Inc, 1934

Rivers attempts unsuccessfully to show how rheumatic fever, rheumatoid arthritis, osteo-arthritis, fibrositis, hypotension, hypertension, the common cold, hay fever, bronchial asthma, pyloric stenosis, catarrhal gastritis, gastric ulcer, gastric carcinoma, dysuria, enuresis, dysmenorrhea, menorrhagia, erythema, urticaria, glaucoma and other diseases and syndromes are closely related to dysfunctions of the autonomic nervous system and are all of a rheumatic syndrome He vaguely refers to amines as the exciting agents He cites his own laboratory and clinical observations, drawing conclusions to support his idea There is no discussion of any detail in the book in regard to the methods and apparatus employed, conditions existing at the time of the studies or any factors that should be made known to the reader He states, however, that his laboratory is insufficiently equipped for thorough and proper experimental studies At the same time, he speaks of the "modern laboratories" with abhorrence and admits unacquaintance with them, so that one is led to think that, though such a laboratory might be proper for careful study, he would be incapable of its use

The book fails to reveal anything new and contains many ungrounded theories falsely presented as facts, many of which may be accepted by the noncritical reader as true There can be no favorable criticisms made in regard to the book

**Accidents chimiothérapiques par hypersensibilité** By Jean Gate, Henri Thiers and Pierre Cuilleret Price, 30 francs Pp 208 Lyon Librairie Scientifique Camugli, 1934

The authors have summarized in this monograph the subject of chemotherapeutic accidents due to hypersensitivity The preface is written by Paul Ravant, who praises the authors highly They have published in French journals many observations which are included in this volume The presentation of the subject matter is divided into four main parts (1) the pathogenesis of medicinal accidents, (2) medicinal hypersensitivity, (3) one hundred and seven observations of medicinal accidents and (4) a discussion of experimental results From the titles listed one may observe the manner in which the material is presented, as well as what is included

The authors do not bring out many new facts or ideas, but present the subject in a systematized manner so that the material is well correlated. Theories and hypotheses of other observers on the subject are discussed and criticized. The monograph is worthy of reading and study.

**The Management of Colitis** By J Arnold Bargaen Edited by Morris Fishbein  
Price, \$3 Pp 235, with 94 illustrations New York National Medical Book Company, Inc., 1935

The modern method of dealing with narrow subjects in monographic form undoubtedly fills a real need. Unfortunately, however, under present economic conditions such books seem to have so small a sale that except as a labor of love on the part of the author there is some question as to whether they serve much practical purpose. The present small volume deals in an interesting and authoritative way with the various types of colitis. Dr Bargaen naturally emphasizes his own work, with which some are not entirely in accord. However, an immense amount of useful material founded on wide experience is assembled here.

**Practical Neurological Diagnosis** By R Glen Spurling Price, \$4 Pp 233, with 99 illustrations Springfield, Ill Charles C Thomas, Publisher, 1935

Nothing except in praise can be said of this admirable compendium. Here in concise form, well illustrated by cuts and diagrams, are set forth the materials for neurologic diagnoses. The collection of the data, the manner of interpreting them so as to localize the lesion and facts bearing on the probable nature of the lesion are briefly outlined. Spurling has succeeded in setting forth clearly and simply material which in most textbooks is presented in an obscure and cumbersome manner.

**Maladies de l'intestin** By R Bensaude Serie III Price, 60 francs Pp 370, with 127 illustrations Paris Masson & Cie, 1935

This volume, which is part of a series, deals systematically with certain rectal diseases—cancer, lymphosarcoma, polyps and rare tumors. The discussion is excellent and up to date, but there is nothing strikingly original which would commend the book especially to English readers. Detailed reports of cases and excellent illustrations are features.

**Verhandlungen der deutschen Gesellschaft für Kreislaufforschung VII**  
Tagung, gehalten zu Bad Kissingen am 16 und 17 April, 1934 Herausgegeben von Prof Dr Eb Koch, Bad Nauheim Paper Price, 15 marks Pp 326, with 65 illustrations and 8 colored plates Dresden Theodor Steinkopff, 1934

This is a collection of forty papers presented before the society at its annual meeting. Again all phases of cardiovascular disease are freely discussed, and much experimental work is reported. As the work on the carotid sinus dominated the meeting in the preceding year, so does a consideration of thrombosis and embolism occupy the forefront this year. Seventeen of the forty papers have to do with thrombosis or embolism or both.

**Experimental Physiology, with Anatomical and Mechanical Illustrations and an Appendix of Technical Data** By Maurice B Visscher and Paul W Smith Price, \$3.25 Pp 191, with 75 illustrations Philadelphia Lea & Febiger, 1935

This laboratory manual for students of elementary physiology offers a good collection of detailed outlines for the performance of the classic experiments in physiology. The illustrations for the most part are diagrammatic and excellent, with the exception of a few photographs of impressive apparatus and of dissections which fail to illustrate. The book appears to add unnecessarily to the cost of medical education in that the printing and binding are better than are necessary in a laboratory guide.



**Laboratory Diagnosis** By Edwin E Osgood Second edition Price, \$6  
Pp 585, with 27 figures and 10 plates Philadelphia P Blakiston's Son &  
Co, 1935

This second edition of Osgood's book on clinical diagnosis seems to the reviewer an extremely satisfactory presentation of the subject. The newer points of view, particularly in regard to the blood, are well assimilated, and throughout the book one finds little with which one could differ. The arrangement of the material in theoretical and practical divisions is convenient, and the thorough index will be of assistance to students. The illustrations are many and well prepared.

# Archives of Internal Medicine

VOLUME 57

JUNE 1936

NUMBLR 6

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## CLINICAL EXPERIENCES IN THE USE OF DETERMINATIONS OF BLOOD IODINE

E PERRY McCULLAGH, M D

AND

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CLEVELAND

In the study of disease of the endocrine glands it is extremely important to be able to determine with accuracy the amounts of hormones present in the body. The results of assays of blood and urine for the amount of estrogenic hormone serve as indexes of the production of ovarian follicular hormone<sup>1</sup>. Assay for testicular hormone in the urine is of considerable assistance in the diagnosis of hypogonadism in the male,<sup>2</sup> and the estimation of the amount of the gonadotropic hormone in the blood and urine by various methods gives a means of estimating the activity of the pituitary gland<sup>3</sup>. The value for blood iodine may be used as a direct indication of the activity of the thyroid gland.

Various methods have been described by which determinations of blood iodine may be made. Modifications of the von Fellenberg technic<sup>4</sup> have been used successfully, but the method requires experience and technical skill and is so time-consuming that it is impracticable for routine clinical use. In 1934 a new method was described by D Roy McCullagh,<sup>5</sup> which is accurate, simpler and more rapid. The results reported

From the Cleveland Clinic

1 Frank, R T, and Goldberger, M A. Clinical Application of the Female Sex Hormone Test, New York State J Med **29** 671 (June 1) 1929. Kurzrok, R. Estimation of Estrin and Follicle-Stimulating Hormone in Urine as Index of Therapy in Menstrual Dysfunction, Endocrinology **16** 361 (July-Aug) 1932.

2 McCullagh, E P, McCullagh, D R, and Hicken, N F. Diagnosis and Treatment of Hypogonadism in the Male, Endocrinology **17** 49 (Jan-Feb) 1933.

3 Fluhmann, C F. Anterior Pituitary Hormone in the Blood During Pregnancy. Preliminary Report, J A M A **92** 1744 (May 25) 1929.

4 von Fellenberg, T. Die Bestimmung kleinster Jodmengen in organischen Materialien, Biochem Ztschr **224** 170, 1930.

5 McCullagh, D Roy. A New Method for the Determination of Iodine, J Biol Chem **107** 35 (Oct) 1934.

here were selected from approximately two hundred determinations of blood iodine which were made in clinical cases by the use of this procedure

The normal value for blood iodine is approximately 10 micrograms per hundred cubic centimeters of blood, therefore 10 cc of blood must be examined to determine the presence of as small an amount of iodine as 1 microgram (0.001 mg). Each iodine level given in the accompanying tables was determined after at least two tests had been made.

Table 1 shows examples of blood iodine levels of patients with diseases which were not related to the thyroid gland. In case 2 some

TABLE 1—*Blood Iodine Values for Patients Without Thyroid Disease*

Case	Sex	Diagnosis	Basal Metabolic Rate, Percentage	Blood Iodine, Micrograms per 100 Cc
1	M	Prostatic hypertrophy	-9, -4	9.5
2	M	Prostatic hypertrophy	-14, -16, -27	7.2
3	M	Mongolism	Impossible	9.1
4	M	Mental deficiency	-16	10.3
5	F	Dyspituitarism	-4, -12	9.7
6	M	Angina pectoris	-10	9.8
7	F	Psychosis	Impossible	10.5
8	F	Psychosis	-17, -9	11.1
9	M	Arterial hypertension	+7	13.2
10	F	Neurocirculatory asthenia	+4	12.5
				Average 10.2

TABLE 2—*Effect of Violent Exercise on the Amount of Iodine in the Blood*

Time in Relation to Exercise	Blood Pressure	Pulse Rate	Respiratory Rate	Blood Iodine, Micrograms per 100 Cc
Before	110/80	64	21	8.0
Immediately after	135/85	148	40	9.2
15 minutes after	115/82	104	23	5.3
45 minutes after	95/75	88	20	6.3
2 hours after	110/90	76	21	6.8

degree of hypothyroidism may have been present. The average level in these patients is comparable to that usually seen in normal persons.

Table 2 shows the effect of strenuous exercise for ten minutes on the blood iodine level of a normal man. The fact that a slight rise was followed by a subsequent fall to a subnormal level suggests that the increase in blood flow caused a temporary "flushing out" of iodine from the thyroid gland. During experiments such as this, the metabolic rate rose in one case to 353 per cent above the normal basal rate. This fact indicates that a knowledge of the basal condition is not necessary when determination of blood iodine is being made to exclude the presence of hyperthyroidism, but it does show that strenuous exercise may cause distinct variation in blood iodine levels.

In table 3 there are shown some blood iodine levels in cases of active hyperthyroidism which were observed clinically. It will be observed that the height of the basal metabolic rate and that of the blood iodine level are not always proportionate to the increased metabolism. In these cases the iodine levels vary from 11.1 to 49.8 micrograms per hundred cubic centimeters of blood.

Table 4 is a tabulation of data from cases in which a clinical diagnosis of hypothyroidism was made because of the presence of typical

TABLE 3—*Blood Iodine Values in Cases of Active Hyperthyroidism*

Case	Basal Metabolic Rate, Percentage	Blood Iodine, Micrograms per 100 Cc
1	+34	25.6
2	+58	42.4
3	+70	20.9
4	+23	24.2
5	+70	11.1
6	+57	21.5
7	+60	28.4
8	+51	38.9
9		49.8
10	+53	38.7

TABLE 4—*Blood Iodine Values in the Presence of Hypothyroidism*

Case	Sex	Basal Meta- bolic Rate, Percentage	Blood Choles- terol, Mg per 100 Cc	Blood Iodine, Micrograms per 100 Cc
1	F	-27	222	8.7
2*	F	-22	224	7.7
3	M	-20	217	6.7
4	M	-16, -14	210	6.6
5	F	-21, -22	230	6.3
6	F	-26, -27		7.5
7	F	-30		7.4
8†	F	-20	277	10.8
9	F	-24, -15	204	6.0
10	F	-30	164	7.6
Average				7.5

\* Progressive exophthalmos

† Thyroid extract had been administered orally until two weeks before the estimation of blood iodine was made

symptoms and signs, a low basal metabolic rate and, in most instances, a relatively high blood cholesterol level. Cases in which hypometabolism was present but in which there was no other evidence of thyroid deficiency were not included in this table. It is interesting to note that in case 2 severe progressive exophthalmos was present, which continued to increase after operation. This is the only case in this group in which studies of the blood iodine were made after operation. In case 8 desiccated thyroid had been taken by mouth until two weeks before the estimation of blood iodine was made. The average blood iodine level in this group of cases was 25 per cent lower than that noted in the cases of non-

thyroid diseases This appears to indicate that the test is of considerably less value in the diagnosis of hypothyroidism than in the diagnosis of hyperthyroidism, especially in individual cases, since the total extent of the change is relatively small This fact, however, does not alter its usefulness in the study of groups of patients who have hypothyroidism

Table 5 includes cases of hypometabolism in which there was no clinical evidence of thyroid disease In cases 2 and 3 the patients were markedly emaciated and had amenorrhea After careful study no plausible explanation for their symptoms was shown other than hypopituitarism Although the value for blood iodine was slightly low in case 1 it scarcely seems proportionate to the low metabolic rate In cases 5 and 6, normal iodine levels were noted

High blood iodine levels have been reported to accompany infections and leukemia, and Curtis<sup>6</sup> found high blood iodine levels in certain patients in whom arterial hypertension was present The administration

TABLE 5—*Blood Iodine Values in Cases of Hypometabolism Not Related to the Thyroid Gland*

Case	Diagnosis	Basal Metabolic Rate, Percentage	Blood Iodine, Micrograms per 100 Cc
1	Narcolepsy	—24	70.60
2	Pituitary cachexia	—42, —40	7.1
3	Pituitary cachexia	—26, —38	11.2
4	Pituitary basophilism	—18, —19	6.6
5	Exhaustion, sexual neurosis	—22	9.7
6	Prepubertal hypogonadism	—16, —27	12.1

of iodine promptly raises the blood iodine level, and the preoperative use of aqueous solution of iodine U S P (Lugol's solution) produces a level of from 500 to 600 micrograms per hundred cubic centimeters In some cases, high blood iodine levels have been found to be inconsistent with the clinical data In all except one of these cases, the patient was in the hospital, where much iodine is used and we believe there had been inadvertent contamination

It has been much more common in our cases thus far to observe high basal metabolic rates associated with normal blood iodine levels than to observe normal metabolic rates associated with high blood iodine levels Table 6 gives two examples of cases of hypertension in which this is true In both these instances hyperthyroidism was suspected In cases 3 and 4 in this table, it is a matter of conjecture whether the metastatic carcinoma caused an elevation of the metabolic rate by producing the effect of an arteriovenous aneurysm or whether the rise in

<sup>6</sup> Curtis, G. M., and Cole, Vera V. The Blood Iodine in Thyroid Disease, *Tr. Am. A. Study Goiter*, 1934, p. 142

the basal metabolic rate was produced by the absorption of toxins. The normal blood iodine level suggests, however, that a diagnosis of hyperthyroidism is made too frequently when malignant disease of the thyroid gland is present. A similar relationship is seen in case 5—an instance of aneurysm of the internal carotid artery. No explanation is offered for the completely normal iodine level in the case of acromegaly.

The determination of blood iodine is sometimes of distinct value in the differential diagnosis of disease of the thyroid gland. This was shown in the cases of arterial hypertension previously cited. In case 1 in table 7 hyperthyroidism was suspected because of clinical evidence

TABLE 6—*Blood Iodine Values in Nonthyroid Hypermetabolism in Which There Was No Evidence of Thyroid Disease*

Case	Sex	Diagnosis	Basal Metabolic Rate, Percentage	Blood Iodine, Micrograms per 100 Cc
1	F	Hypertension (280/165)	+55, +55	7.0
2	F	Hypertension (190/140)	+53, +36	8.1
3	F	Malignant goiter, metastases	+28, +41	10.3
4	F	Malignant goiter, metastases	+29, +26	61.74
5	M	Aneurysm of internal carotid artery	+22, +17	95.96
6	F	Acromegaly, goiter	+20, +26	90.90

TABLE 7—*Blood Iodine Values as an Aid in Differential Diagnosis*

Case	Disease Suspected	Diagnosis	Basal Metabolic Rate, Percentage	Blood Iodine, Micrograms per 100 Cc
1	Hyperthyroidism	Neurocirculatory asthenia	+20, -5	99.90
2	Cretinism	Congenital mental deficiency	-16	10.3
3	Cretinism	Cerebral injury		13.0
4	Hyperthyroidism	Neurocirculatory asthenia	-7, -8	12.0
5	? Hyperthyroidism	Encephalitis		11.7
6	Hyperthyroidism	Hypo ovarianism	+12, +12	7.1
7	Hyperthyroidism	Simple goiter	+21, -12	12.5

and because the basal metabolic rate on the first determination was +20 per cent. The diagnosis was revised, however, when the blood iodine level was repeatedly found to be normal. Subsequently the basal metabolic rate was -5 per cent. A similar occurrence was seen in case 7, in which the patient was a very active, rather excitable girl, 12 years of age, who had a tendency to tachycardia, and in whom the results of the first metabolism test confused the clinical picture further, since hyperthyroidism had been suspected. In cases 2 and 3 a diagnosis of cretinism was ruled out because of clinical findings and because normal epiphyseal growth was revealed by the roentgenogram. Normal values for blood cholesterol and for blood iodine formed good corroborative evidence. In case 3, the fact is demonstrated that the blood iodine level may help to exclude the presence of hyperactivity of the thyroid

gland in cases in which it is impossible to determine the basal metabolic rate in young children. By means of determinations of blood iodine the possible diagnosis of hyperthyroidism was excluded in case 5, also, when cooperation could not be obtained for making a test of metabolism. In case 6, symptoms associated with the menopause simulated those of hyperthyroidism, but the correct diagnosis was made after the blood iodine was measured.

#### SUMMARY

From a study of these cases, it is indicated that in Cleveland the blood iodine levels of normal adults and of patients who have diseases which are not associated with the thyroid gland range from approximately 8 to 12 micrograms per hundred cubic centimeters.

The blood iodine level is very high in cases in which iodine medication has been instituted. Exercise has little influence in raising the level of blood iodine, but strenuous exertion may have a temporarily depressing effect.

Under controlled conditions the blood iodine level is proportionate to thyroid activity in most cases, the change in the level, however, being relatively greater in persons with hyperthyroidism than in those with hypothyroidism.

Determinations of blood iodine are of value in the differential diagnosis of hyperthyroidism.

# EXPERIMENTAL DIABETES INSIPIDUS IN THE MONKEY

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The experimental production of diabetes insipidus in a large series of cats has been reported, and the various phases of the problem of the etiology of this condition have been discussed in a series of recent publications<sup>1</sup> It is sufficient for the present to state that polyuria of long duration has always been found, in our experience, in association with lesions of the hypothalamus placed so as to interrupt the bundle of unmyelinated fibers which runs from the nucleus supra-opticus down the infundibular stalk into the pars posterior of the hypophysis In these cases atrophy of the supra-optic nucleus and of the pars nervosa has been a striking feature of the changes observed at autopsy The development and course of the polyuria in cats are characteristic Usually, although not always, the operation is followed by the immediate onset of a transient polyuria, which subsides after from one to four days From eight to fifteen days after operation (the so-called latent period) the permanent phase of the polyuria develops, and it continues with some fluctuation, and in varying degrees of intensity in different subjects, until the animal is killed This polyuria can be controlled by the administration of pitressin and can be greatly influenced by the feeding of thyroid substance and sodium chloride<sup>1c</sup>

So far as we know, the production of experimental diabetes insipidus in monkeys has not been reported, although it is desirable that this animal should be used on account of its closer relationship to the human species Therefore, a group of macaques was operated on, and the subsequent occurrence of diabetes insipidus in two of them is reported here

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This work was aided by a grant from the Rockefeller Foundation

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1 (a) Fisher, C, Ingram, W R, and Ranson, S W The Relation of the Hypothalamico-Hypophyseal System to Diabetes Insipidus, *Arch Neurol & Psychiat* **34** 124 (July) 1935 (b) Fisher, C, Ingram, W R, Hare, W K, and Ranson, S W The Degeneration of the Supra-Optico-Hypophyseal System in Diabetes Insipidus, *Anat Rec* **63** 29 (Aug 25) 1935 (c) Fisher, C, and Ingram, W R The Effect of the Feeding of Thyroid Extract or Salt and of Thyroidectomy on the Fluid Exchange of Cats with Diabetes Insipidus, to be published



## METHODS

Young specimens of *Macaca mulatta* weighing between 2 and 3 Kg were used

The lesions in the hypothalamus were produced electrolytically with the aid of the Horsley-Clarke stereotaxic instrument. After operation the animals were placed in metabolism cages, and the output of urine and the consumption of water were measured daily. The food consisted of fresh vegetables and fruit in as nearly constant quantities as possible, with the addition of 120 cc of milk each day. Trouble was experienced in the early experiments because of the tendency of the monkeys to spill their water. This was largely obviated by the use of reservoir jars, which were placed above the cages and which fed water as needed into small cups anchored to the wall and floor of the cage. Indications of spilling could then be checked by examination of a small quantity of talcum powder sprinkled on the drain pan just beneath the water cup. The specific gravity of the urine as determined with an ordinary urinometer was recorded each day.

## RESULTS

Diabetes insipidus developed in two of the eight monkeys used in these experiments. One of these (MD 9) showed a decided increase in the average output of urine, the average volume before operation being 266 cc, which corresponds closely with the average for the seven normal monkeys, and that after operation being 749 cc (table). The other (MD 5) showed more moderate polyuria, the output of urine after operation averaging 485 cc. The remaining monkeys showed no significant increase, on the other hand, four of them had a diminished volume of urine after operation, while their intake of water was markedly reduced. The results in general are summarized in the table, but it should be pointed out that the figures for the intake of water for the first four animals must be considered to be only approximate, owing to difficulties of measurement during the period of observation. The discrepancies between the output of urine and the intake of water may be considered to be made up by the consumption of milk and in some cases by the amount of water contained in the food. Accurate measurement of the consumption of milk was, for various reasons, not possible, usually from 50 to 120 cc was taken. Also the average figures for MD 5 and MD 9 do not represent quite the full degree of the polyuria, as the output of urine during the latent period between operation and the onset of the polyuria was included, as was also the output during the two days when no water was given. The average daily output of urine during the permanent phase of the polyuria, excluding the two days of deprivation of water, was 577 cc for MD 5 and 851 cc for MD 9.

The course of the polyuria shown by MD 5 and MD 9 is of some interest.

In the case of MD 5 there was no evident transient phase, the output of urine immediately after operation remaining within the normal range. However, the

consumption of water dropped to zero on the fourth, fifth and sixth postoperative days. The polyuria developed rather suddenly on the fourteenth day, when the volume of urine increased from 250 cc to 500 cc, and the intake of water jumped from 225 cc to 475 cc. Some occult change may have preceded this sudden change in actual volume, since the specific gravity was unusually low (1.006) for two days before the onset of the polyuria. During the latent period the output of urine averaged 271 cc, with a specific gravity of 1.009, and the consumption of water averaged 153 cc. During the permanent phase the average daily output of urine exclusive of that on the two days on which no water was given, was 577 cc, with a specific gravity of 1.004, and the consumption of water averaged 487 cc. Attempts to control the polyuria in this animal with pitressin were disappointing, but it was later found that the preparation we were using was relatively inactive. Deprivation of water reduced the output of urine from 620 cc to 235 cc, and 135 cc on successive days.

### Average Output of Urine

Monkey	Average Output of Urine Before Operation, Cc	Average Specific Gravity Before Operation	Average Output of Urine After Operation, Cc	Average Specific Gravity After Operation	Average Water Intake Before Operation, Cc	Average Water Intake After Operation, Cc	Days Observed After Operation
Monkeys Without Polyuria*							
MD 1	216	1.011	246	1.012	140	103	15
MD 2	227	1.012	163	1.011	104	20 (?)	15
MD 3	273	1.011	161	1.014	203 (?)	12	21
MD 4	298	1.009	149	1.014	268 (?)	8	20
MD 10	207	1.013	293	1.011	94	56	39
MD 11	307	1.009	255	1.009	179	96	25
Monkeys With Polyuria							
MD 5			485†	1.005		412†	58
MD 9	266	1.011	749†	1.005	160	585†	85

\* Seven normal monkeys showed an average output of urine of 256 cc, with a specific gravity of 1.011.

† Including the latent period and two days when no water was given and periods when pitressin was administered.

MD 9 gave clear evidence of transient polyuria. On the three days following operation the volumes of urine were 540, 570 and 500 cc, with specific gravities of 1.005, 1.005 and 1.007, respectively. The quantities of water consumed during these three days were 475, 550 and 250 cc. The output of urine then declined to a low normal level, reaching 100 cc (specific gravity 1.022) on the seventh postoperative day. The consumption of water also dropped, reaching zero on the eleventh and twelfth days. The onset of the permanent phase was more gradual in this instance, but on the thirteenth day the volume of urine increased from 375 cc to 470 cc, and the consumption of water rose from 0 to 335 cc. The exchange of water then rose rapidly to a high level, which persisted during the period of survival of the animal. The average daily output of urine during the permanent phase, exclusive of the two days on which no water was given, was 851 cc, the specific gravity was 1.0048, and the average consumption of water was 664 cc. The peak output of urine was 1,220 cc, and volumes over a liter were observed on seventeen occasions. On the two days during which the animal was deprived of water the output of urine dropped from 850 cc to 590 cc and 200 cc on successive days. The averages include several days during which pitressin was administered. The matter of the effect of pitressin deserves special mention at this point.

On several occasions pitressin, which was later found to be deficient in activity, was injected. This had a relatively slight effect on the polyuria, the output of urine at one time dropping from 780 to 525 cc. The striking thing, however, was the marked rebound rise which followed the cessation of injection, on the day following the administration of pitressin the volume of urine rose from 525 to 1,150 cc. Shortly before MD 9 was killed an active preparation of pitressin was obtained<sup>2</sup>. This was found to have a marked but evanescent effect. On January 30, 0.66 cc of pitressin was injected subcutaneously in two doses, 0.33 cc at 10 30 a m and 0.33 cc at 4 p m. During the period from 10 30 a m to 9 p m only 150 cc of urine was excreted, but during the night the output of urine returned to a very high level, and 560 cc was produced. On January 31, 1 cc of pitressin was given in three doses of 0.33 cc at 9 30 a m, 1 30 p m and 4 45 p m. From 9 30 a m to 5 p m only 25 cc of urine was excreted and no water was drunk, but between 5 p m on January 31 and 9 a m on February 1, 375 cc (specific gravity 1.010) was produced. During the next twenty-four hours the volume of urine was 850 cc (specific gravity 1.005). It will be seen that when the animal was under the influence of these small doses of pitressin it became practically anuric but that during the night, presumably as the effects of the drug passed off, a fair rate of excretion of urine was resumed. This night sample had a relatively high specific gravity, however, and it was probably not until the next day that the polyuria was in full swing again.

#### ANATOMIC FINDINGS

Examination of the sectioned brain stems of the monkeys of this series showed that in MD 5 and MD 9 the lesions were placed so as to interrupt the supra-optico-hypophyseal tract, with concomitant atrophic changes in the supra-optic nuclei and in the pars posterior of the hypophysis. In the animals in which the results were negative, the lesions either did not affect this system or encroached on it so slightly that very little atrophy occurred in the supra-optic nuclei and the posterior lobe of the pituitary. It is significant, however, that in these animals lesions in the hypothalamus which differed little from those in MD 5 and MD 9 but which did not interrupt the supra-optico-hypophyseal tract did not produce polyuria. Furthermore, in a large group of monkeys used for other experiments, lesions have been placed throughout the extent of the lateral hypothalamic area and in the medial and lateral portions of the posterior hypothalamic region, including the region of the mamillary bodies, and no tendency to polyuria has been observed.

A brief statement as to the anatomy of the hypothalamico-hypophyseal system in the normal monkey may facilitate the description of the experimentally produced lesions.

*The Hypothalamico-Hypophyseal Fiber System in the Monkey*—The nucleus supra-opticus in the monkey lies just rostral and dorsal to the

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2 This preparation was supplied by Dr. Oliver Kamm, of Parke, Davis & Co.

beginning of the optic tract, with a medial and vential component caudal to the chiasm. In sagittal sections of the hypothalamus stained by the pyridine silver method this nucleus is seen to give rise to a rather heavy bundle of fibers which passes caudomedially over the dorsal surface of the optic chiasm and also apparently to send a number of fibers directly into the dorsal portion of the latter. The more superficial bundle becomes heavier as it passes medioventrally, presumably as fibers from other portions of the hypothalamus, including the ventromedial portion of the supra-optic nucleus, join it. A number of fibers which come from some point dorsal and medial to the supra-optic nucleus also join the tract—these may arise in the paraventricular, or filiform, nucleus (Roussy and Mosinger<sup>3</sup>). The exact origin of the fibers which enter the tract from areas caudal to the supra-optic nucleus could not be determined with exactitude, apparently most of them arise in the ventromedial hypothalamic nucleus, with comparatively few coming from the more posterior nuclei. As the fibers approach the ventral surface of the brain stem they turn almost directly mediad and pass into the walls and floor of the infundibulum, converging toward the pituitary stalk mediocaudally. Near the midline a heavy component appears coursing down the anterior wall of the infundibulum, these fibers appear to come from the dorsocaudal part of the chiasm. If such is the case, it is logical to assume that they are the continuations of the fibers which seemed to pass from the supra-optic nucleus directly into the chiasm. In this connection one may recall the remark of Papez and Aronson<sup>4</sup> à propos the apparent connection of the supra-optic nucleus with fibers of the optic system. Greving<sup>5</sup> also described a supra-optico-thalamic tract which was said to rise in the optic chiasm and to pass through the supra-optic nucleus on its way to the thalamus. However, with the preparations available at present one cannot exclude the possibility that this rostromedial component may be formed by the condensation of scattered fibers which have taken a more dorsal course from the supra-optic or other nuclei. A possible pathway through the chiasm, however is indicated by a broken line in figure 4. Once gathered in the infundibulum, the fibers pass as a very heavy tract down the pituitary stalk into the pars nervosa, where they divide and scatter into an enormously complex meshwork which spreads among characteristic groups or islets of cells which are presumably identical with the pituicytes described

3 Roussy, G., and Mosinger, M. Rapports anatomiques de l'hypothalamus et de l'hypophyse, *Compt rend Soc de biol* **112** 557, 1933

4 Papez, J. W., and Aronson, L. R. Thalamic Nuclei of *Pithecus* (Macacus) *Rhesus*. I. Ventral Thalamus, *Arch Neurol & Psychiat* **32** 1 (July) 1934

5 Greving, R. Die Fasersysteme des Hypothalamus, in Müller, L. R. *Lebensnerven und Lebenstrieb*, ed 3, Berlin, Julius Springer, 1931, p 150

by Bucy<sup>6</sup> The islet structure is characteristic of the normal pars nervosa We are unable to say whether any of these fibers enter the pars intermedia in the monkey, although small numbers of them have been said to do so in man (Bucy<sup>6</sup>) and in the cat (Fisher et al<sup>1b</sup>) Figure 3 illustrates the appearance of the normal supra-optico-hypophyseal tract in the infundibular stalk of the monkey

It will be seen that hypothalamic lesions designed to interrupt the supra-optico-hypophyseal tract must cover a rather wide area and that those placed at the opening of the infundibulum, where the fibers converge, have the best chance of producing complete destruction of this system (fig 4)

It has been pointed out<sup>1b</sup> that the innervation of the posterior lobe of the pituitary gland has two main constituents, these together being called the hypothalamic-hypophyseal tract The first of these arises from the supra-optic nuclei and is designated the supra-optico-hypophyseal tract, the other comes from cell groups farther caudad and may be called the tubero-hypophyseal tract Figure 4 is a diagrammatic representation of the hypothalamico-hypophyseal system in the monkey

*The Lesions in Monkeys in Which Diabetes Insipidus Did Not Develop—*  
MD 1 Cross-sections stained with cresyl violet showed the lesions to be placed well caudal to the beginning of the stalk, bilaterally, affecting the ventromedial hypothalamic nuclei, extending caudad to destroy most of the premamillary region and destroying the right mamillary body almost completely

MD 2 Cross-sections stained with cresyl violet showed the lesions to be situated bilaterally, on the ventral surface of the hypothalamus (fig 1 A) just caudal to the pituitary stalk, extending caudad into the ventral portion of the pre-mamillary area and terminating just ventral to the rostral border of the mamillary bodies The supra-optic nuclei, pituitary stalk and hypophysis were normal in appearance

MD 3 Cross-sections showed that the bilateral lesions encroached slightly on the caudal border of the chiasm and extended caudad on the ventral surface of the hypothalamus, meeting in the midline just above the infundibulum Farther caudad the tuber cinereum proper and the mamillary bodies were largely destroyed and the right lateral hypothalamic area was encroached on, but the supramamillary area remained intact The dorsal wall of the infundibular recess was thin, but the ventral part of the stalk was well developed There was a moderate increase in the number of cell nuclei in the pars nervosa of the pituitary body, indicating some involvement of the tubero-hypophyseal fibers The supra-optic and filiform nuclei were large and well developed and were of normal cell structure, indicating integrity of their fibers, although it was not clear how the latter escaped at least partial destruction

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6 Bucy, P C The Hypophysis Cerebri, in Penfield, W Cytology and Cellular Pathology of the Nervous System, New York, Paul B Hoeber, Inc, 1932, vol 2, p 765



MD 4 Cross-sections showed that the rostral extent of the lesions affected the ventral surface of the optic chiasm. There was a small area of softening just dorsal to the chiasm in the midline. Caudally the lesions lay at the ventral surface of the hypothalamus just dorsal to the beginning of the infundibulum but did not meet in the midline, leaving room for the passage of supra-optico-hypophyseal fibers (fig 1 B). The ventromedial hypothalamic nuclei were severely

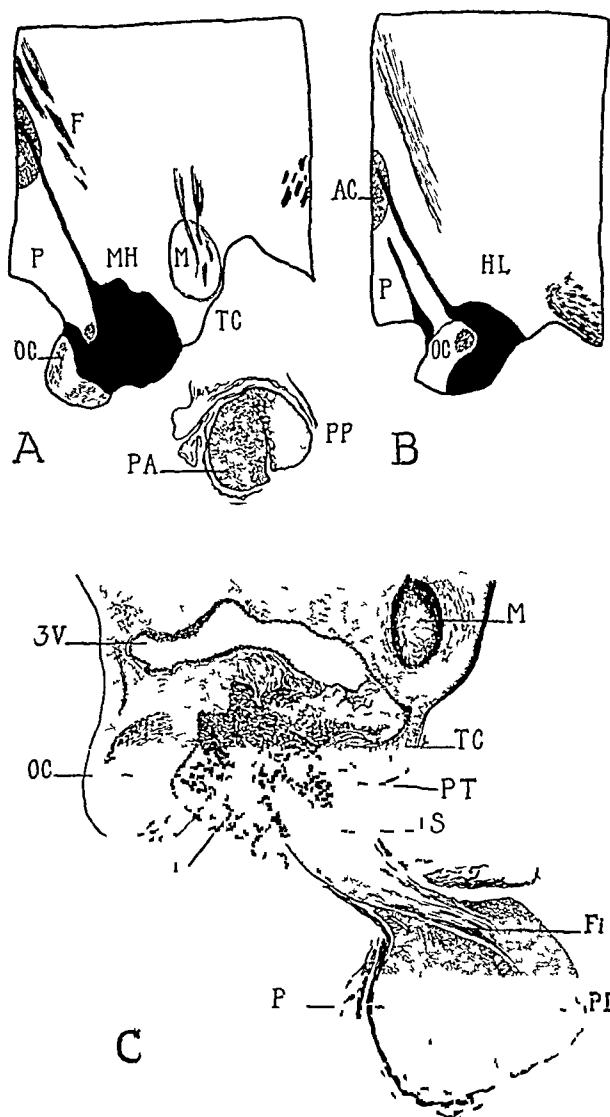


Fig 2—A, drawing showing the location of lesions on the left side of the brain in MD 9, in which polyuria developed. Sagittal sections prepared with pyridine silver. B, drawing showing the lesions on the right side of the brain in MD 9. C, drawing of sagittal section of the hypothalamus and hypophysis of MD 9 stained with pyridine silver, showing the lesion and degeneration of the supra-optico-hypophyseal tract. Compare with figure 3 which shows a normal tract.

damaged, and there was slight damage to the premamillary area. The supra-optic nuclei were large and well developed. The pituitary stalk was well developed but

showed slight gliosis. The posterior lobe of the hypophysis was of normal size and showed a relatively slight increase in the number of cell nuclei.

MD 10. Cross-sections showed that on the left side the lesions lay just caudal to the chiasm, destroying the ventromedial portion of the supra-optic nucleus and extending dorsad as far as the tip of the third ventricle. The pars tuberalis was partially destroyed on the left side, and the left wall of the infundibulum was damaged. The lesion extended caudad into the premamillary area. On the right side the lesions were farther from the midline and affected especially the ventral surface of the optic tract. The chief damage on this side was an area of softening (probably of vascular origin) which destroyed the lateral hypothalamic area caudal to the ventromedial component of the supra-optic nucleus and which extended dorsad into the anterior part of the dorsal thalamus and the anterior limb of the internal capsule. This damage extended caudad as far as the mamillary bodies, the right one of which was atrophic because of the inter-

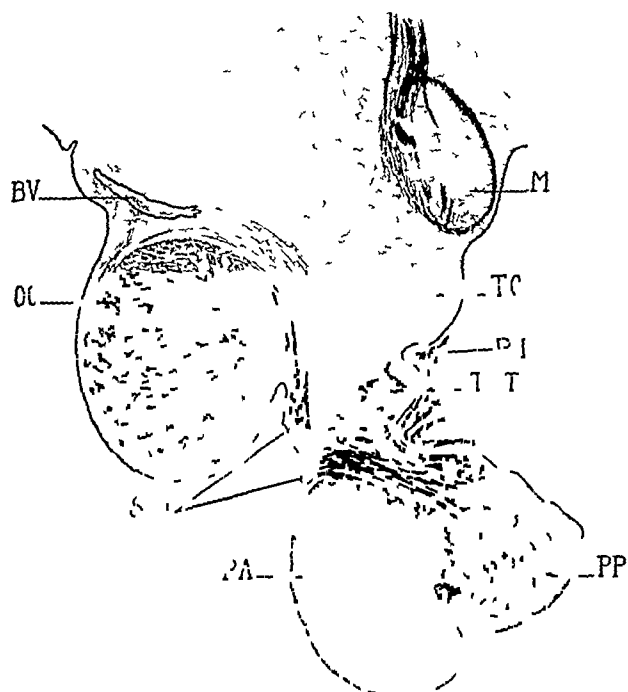


Fig 3—Drawing of sagittal section of hypothalamus and hypophysis prepared with pyridine silver, showing the normal hypothalamico-hypophyseal fiber system in MD 11. Compare with figure 2 C.

ruption of the fornix and the mamillothalamic tract. The left supra-optic nucleus was atrophied, the right, especially its ventromedial component, was well developed. The posterior lobe of the pituitary gland showed a mild increase in the number of cell nuclei.

MD 11. Sagittal sections stained with pyridine silver showed the electrolytic needle to have passed clear through the diencephalon with a minimum of damage to the hypothalamus, there being no electrolytic lesions in the brain substance. Although there was a very extensive area of softening in the right dorsal thalamus and corpus striatum, the hypothalamico-hypophyseal system was unaffected and furnished a good example of the normal condition (fig 3).

*The Lesions in Monkeys with Diabetes Insipidus*—MD 5. Cross-sections stained with cresyl violet showed that the lesions extended well forward through the optic chiasm, which was largely destroyed, producing some damage dorsal to





Many of these came from the caudal portion along the ventral surface of the tuber, others came from the region of the ventromedial hypothalamic nucleus, all could be traced into the infundibulum

The damage produced by the lesions on the other side extended mediad to the midline on the posterior border of the chiasm, destroying the ventromedial portion of the supra-optic nucleus and encroaching on the anterior wall of the infundibulum, the cavity of which contained many large cells (phagocytes or fibroblasts) This damaged area extended dorsad as far as the floor of the third ventricle to the left of the midline and ventrad encroached on the pituitary stalk, which contained a sparse scattering of fibers Laterally the lesions were sufficiently extensive to include part of the ventromedial hypothalamic nucleus and to damage the chiasm severely (fig 2 A) The latter, although atrophic (compare figs 2 C and 3), contained some fibers on this side The lesions were less extensive farther laterally but persisted in the caudal part of the chiasm and in the immediate post-chiasmatic and suprachiasmatic regions The supra-optic nucleus was atrophic, containing only shrunken, abnormal cells, and very few fibers issued from it The pituitary stalk contained relatively few fibers, which were evidently of tuberal origin, since the supra-optic fibers were completely absent (compare figs 2 C and 3) The posterior lobe of the hypophysis was somewhat decreased in size and showed a rather uniform structure, the normal islet formation and massive mesh-work of fibers being absent

The hypophysis was unaffected directly by the lesion in MD 5, the pars tuberalis, the pars intermedia and the pars anterior appearing normal in the sections stained with cresyl violet There was some damage to the pars tuberalis in MD 9, but so far as could be determined in the preparations stained with pyridine silver the pars anterior and the pars intermedia were normal

#### COMMENT

The results described show that the syndrome of diabetes insipidus can be produced experimentally in the monkey by a technic similar to that used in the cat The polyuria thus produced follows a course similar to that in the cat, the onset of the permanent phase of the increase in water exchange being preceded by a latent period during which polyuria of transient character may occur The etiology of the latter is still in doubt, although it has been suggested that it may be due to irritative processes consecutive to the placing of the lesion (Fisher, Ingram and Ranson,<sup>1a</sup> Ingram and Barris<sup>7</sup>) The occurrence of a latent period is also of interest, further evidence for such a period being found in the protocols of other experimenters who have succeeded in producing diabetes insipidus in animals and one clinical case of diabetes insipidus of traumatic origin having been reported in which there was a latent period of twelve days before the development of the polyuria (Ciminata<sup>8</sup>)

The most interesting thing in relation to the experimental production of polyuria is the uniform involvement of the supra-optico-

<sup>7</sup> Ingram, W R, and Barris, R W Diuresis Associated with Direct Stimulation of the Hypophysis, *Endocrinology* **19** 432 (July-Aug) 1935

<sup>8</sup> Ciminata, A Sulla regolazione idrica e salina nell'uomo, in rapporti al diabete insipido, *Fisiol e med* **2** 641, 1931

hypophyseal system in all our subjects, which now comprise some thirty cats besides the two monkeys. A relatively complete or very severe destruction of this system is essential, for it has been found that unilateral or partial damage is without result in cats and monkeys. There is apparently some correlation between the intensity of the polyuria and the amount of involvement, beyond a certain level, of the supra-optico-hypophyseal system, in certain subjects at least. The intense polyuria in MD 9 was associated with complete destruction of the tract and with marked atrophy of the supra-optic nucleus. In MD 5, which had a more moderate volume of urine, while there was noteworthy atrophy of the nucleus, it was not comparable with that in MD 9, indicating the escape of some fibers. The participation of this system in the regulation of water metabolism is not illogical when one recalls the numerous clinical cases in which diabetes insipidus has been consecutive to destruction of the posterior lobe of the hypophysis and the fact that extracts of this portion of the pituitary are effective in controlling the polyuria. If one considers a normal innervation of the posterior lobe to be necessary for the production or release of substances influencing the water metabolism of the body, the interruption of this innervation can then be held to produce a deficiency which is responsible for the excessive exchange of water. This idea has been advanced by Greving<sup>9</sup> on theoretical grounds as a partial explanation of the phenomenon, after the original suggestion of Kary,<sup>10</sup> and a neurohormonal hypothesis has been adopted by Roussy and Mosinger,<sup>11</sup> although in reports of earlier work Camus, Roussy and Le Grand<sup>12</sup> expressed the view that the hypothalamus alone is involved, without participation of the pituitary. Support for Greving's suggestion is found in the work of Broers,<sup>13</sup> who found it possible to produce polyuria in dogs by destruction of the supra-optic nuclei or by interruption of the infundibular stalk. From the standpoint of direct glandular intervention, Richter<sup>14</sup> recently pro-

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9 Greving, R. Zwischenhirn-Hypophysensystem, in Muller, L. R. *Lebensnerven und Lebenstrieb*, Berlin, Julius Springer, 1931, p. 188.

10 Kary, C. Pathologisch-anatomische und experimentelle Untersuchungen zur Frage des Diabetes insipidus und der Beziehungen zwischen Tuber cinereum und Hypophyse, *Virchows Arch f path Anat* **252** 734, 1924.

11 Roussy, G., and Mosinger, M. Le tuber cinereum et son rôle dans les principales fonctions du métabolisme. *Métabolisme de l'eau, des glucides et des lipides*, *Ann de med* **33** 301, 1933.

12 Camus, J., Roussy, G., and Le Grand, A. Etude anatomo-pathologique des lésions expérimentales provoquant le syndrome polyurique et le syndrome adiposogénital chez le chien, *Compt rend Soc de biol* **86** 1070, 1922.

13 Broers, H. Experimentele Diabetes Insipidus, *Inaug Dissert*, Utrecht, Kemink en Zoon, 1932.

14 Richter, C. P. Experimental Diabetes Insipidus. Its Relation to the Anterior and Posterior Lobes of the Hypophysis, *Am J Physiol* **110** 439, 1934.

duced polyuria in a large number of rats by complete removal of the posterior lobe of the pituitary gland, the occurrence of the polyuria apparently being conditioned by the persistence of at least a major part of the anterior lobe in attachment to the brain. Other evidence can be adduced by a study of the older literature, in which permanent polyuria in animals is reported to have been associated with separation or compression of the pituitary stalk, detachment or atrophy of the posterior lobe or lesions in the infundibular or preinfundibular portion of the hypothalamus. It is, perhaps, not out of place to suggest that removal of the posterior lobe of the pituitary gland must be carried out with great care, as it has been found that relatively small remnants of this structure are sufficient to prevent the occurrence of polyuria, provided they remain in connection with the infundibular stalk (Fisher, Ingram, Hare and Ranson<sup>1b</sup>). Our finding of atrophy and an increased number of cell nuclei of the posterior lobe of the pituitary gland finds some parallel in the clinical findings of Davison and Selby,<sup>15</sup> who reported gliosis of the posterior lobe in a case of mild diabetes insipidus, and of Kraus<sup>16</sup> who mentioned a case in which the posterior lobe was rich in nuclei.

Numerous cases in which complete removal of the hypophysis has not been followed by polyuria necessitate still further explanation, however. These have led to the suggestion of von Hann<sup>17</sup> that the presence of active tissue of the anterior lobe of the hypophysis is a necessary prerequisite to the development of diabetes insipidus. Richter's<sup>14</sup> work supported this idea, and cases have been described in the literature in which diabetes insipidus has disappeared as a growing neoplasm has encroached on the pars anterior. The outstanding contrary evidence is the appearance of polyuria, which is said to follow the production of hypothalamic lesions in animals from which the hypophysis apparently had been removed (Camus, Roussy and Le Grand,<sup>11</sup> Broers<sup>12</sup>). Recently Biggart<sup>18</sup> reported three cases of diabetes insipidus in which the condition was explained on the basis of interruption of the supra-optico-hypophyseal tract, in one by a surgical injury just behind the chiasm, in one by an adenocarcinoma which destroyed the posterior lobe and stalk and in one by encephalitis, which destroyed the supra-optic nuclei. In the third case the patient was refractory to treatment with

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15 Davison, C., and Selby, N. E. Hypothermia in Cases of Hypothalamic Lesions, *Arch Neurol & Psychiat* **33** 570 (March) 1935

16 Kraus, E. J. Die morphologischen Veränderungen der menschlichen Hypophyse nach Zerstörung der Zwischenhirnbasis bzw. des Hypophysenstiels und deren Folgen, *Virchows Arch f path Anat* **286** 656, 1932

17 von Hann, F. Ueber die Bedeutung der Hypophysenveränderungen bei Diabetes Insipidus, *Frankfurt Ztschr f Path* **21** 337, 1918

18 Biggart, J. H. Diabetes Insipidus, *Brain* **58** 86, 1935

posterior pituitary, a finding explained by the extensive destruction of the tuberal nuclei by the disease. It was suggested that the normal site of action of the antidiuretic hormone of the posterior lobe of the pituitary gland was on the nuclei of the posterior part of the hypothalamus—since these were destroyed, treatment with posterior pituitary was ineffective. This, however, presumes a purely nervous mechanism from this point on, and it has been found that denervation of the kidneys (Bailey and Bremer,<sup>19</sup> Houssay and Carulla,<sup>20</sup> Camus and Gournay<sup>21</sup>) and section of the cervical portion of the spinal cord and the vagi (Bourquin<sup>22</sup>) have no significant effect on polyuria in dogs. Furthermore, it would follow that extensive lesions of the region of the tuber would produce diabetes insipidus. This we hesitate to accept, since in many cats extensive damage to the posterior portion of the hypothalamus has failed to be followed by polyuria. The same is true in monkeys (MD 1, MD 2, MD 3, MD 10). Also, it has been found possible in our experience to diminish by the use of pitressin the polyuria of cats in which the lesions not only interrupted the supra-optico-hypophyseal system but extended into the posterior part of the hypothalamus. Biggart's case might perhaps be explained by assuming the polyuria to be due to an irritation accompanying the active encephalitis, so intense as to overcome the antidiuretic effects of posterior pituitary. Some support for this suggestion is found in experiments of Camus and Roussy<sup>23</sup> in which they found that there was an initial phase of the polyuria during which hypophyseal extracts had no marked effect and a permanent phase in which the extracts lowered the output of urine. These phases may correspond to our transient and permanent periods of polyuria.

It would perhaps be going too far at the present time to state that interruption of the supra-optico-hypophyseal system is the only factor involved in the production of diabetes insipidus, although the constant occurrence of its involvement in a large number of cases of experimental polyuria and its integrity in cases in which polyuria is not present can hardly be considered to be mere coincidence. Further factors, especially those on the positive side—the actual causes of the excessive exchange of water—await investigation.

19 Bailey, P., and Bremer, F. Experimental Diabetes Insipidus, *Arch Int Med* **28** 773 (Dec.) 1921.

20 Houssay, B. A., and Carulla, J. E. Polyurie par piqûre cerebrale chez les chiens a reins enerves, *Compt rend Soc de biol* **85** 1252, 1920.

21 Camus, J., and Gournay, J. J. La polyurie tuberienne apres enervation des reins, *Compt rend Soc de biol* **88** 694 1923.

22 Bourquin, H. Studies on Diabetes Insipidus. I, *Am J Physiol* **79** 362 (Jan.) 1927.

23 Camus, J., and Roussy, G. Diabete insipide experimental et opotherapie hypophysaire, *Compt rend Soc de biol* **83** 1578, 1920.

# STUDIES ON NITROGEN AND SULFUR METABOLISM IN BRIGHT'S DISEASE

## VII SULFUR CONTENT OF URINARY PROTEIN

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In a study of the nitrogenous exchange of patients with Bright's disease, it was suggested by Peters that the nonprotein nitrogen content of the urine provides more significant data than the total nitrogen content of the urine. In the course of experiments designed to test the validity of this suggestion and others, we studied the total amounts of nitrogen and sulfur and compared these figures with the values for the total nonprotein nitrogen and nonprotein sulfur in the urine of patients with albuminuria.

The difference between the total nitrogen and sulfur content of the urine as voided and that of the protein-free filtrate of the same specimen of urine gives the nitrogen and sulfur content of the protein excreted. We were struck with the low sulfur content of the protein excreted by patients with "nephrosis" and extended the investigation to include the study of other types of proteinuria.

To determine the validity of the method we carried out the following procedure:

The proteins were precipitated by heat and acetic acid. Care was taken to bring the mixture just to the boiling point and to avoid prolonged boiling. Usually 300 cc of urine was used, to which 1 cc of a 0.5 per cent solution of acetic acid was added if the urine was acid and more if the urine was alkaline, although almost all the specimens of urine the analyses of which are reported in this paper were acid. The mixture was brought to a boil and was filtered while hot after the precipitate was allowed to settle. It was noted that the protein in the urine of the patients with "nephrosis" formed a distinctive coagulum the character of which differed from that in the urine of other persons. Since such treatment obviously denatures the protein, it seemed desirable to check the validity of the method with protein obtained without denaturation. Therefore, a specimen of urine was dialyzed, and the protein so obtained was dried and analyzed.

In the accompanying table are shown the results of the determinations carried out by calculation of the difference between the nitrogen

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From the Medical Clinic of the Peter Bent Brigham Hospital

Aided by a grant from the Proctor Fund for the Study of Chronic Diseases of the Harvard University Medical School

and sulfur content of the urine as voided and that of the protein-free filtrate, and by analysis of the precipitated protein and of the dialyzed protein. It will be seen that the results of these analyses agree with reasonable accuracy. It is therefore apparent that denaturation of the protein produced by heat coagulation does not affect the sulfur content. Consequently it seemed valid to apply the simplest method, that of determination by difference, to various conditions in which proteinuria is present.

There exist only a few analyses of human serum albumin for sulfur content, but it is generally stated that the sulfur content is approximately from 1 to 2 per cent. Since the nitrogen content is close to 16 per cent, normal serum albumin presents a nitrogen-sulfur ratio of between 8.1 and 16.1. It is evident that the protein referred to in the table bears only a remote relationship to that of normal serum albumin, at least so far as its sulfur content is concerned.

*Results of Analysis of the Nitrogen and the Sulfur Content of Urinary Protein by Three Methods\**

Material Analyzed	Nitrogen Content	Sulfur Content	Nitrogen Sulfur Ratio
Urine as voided	8.33 Gm	282 mg	30
Protein free urine filtrate	6.78 Gm	276 mg	25
Urinary protein			
By difference	1.55 Gm	6 mg (0.06%)	259
Coagulum (heat + acetic acid 0.5%)	80.2 mg	0.32 mg (0.06%)	251
By dialysis	80.5 mg	0.35 mg (0.07%)	230

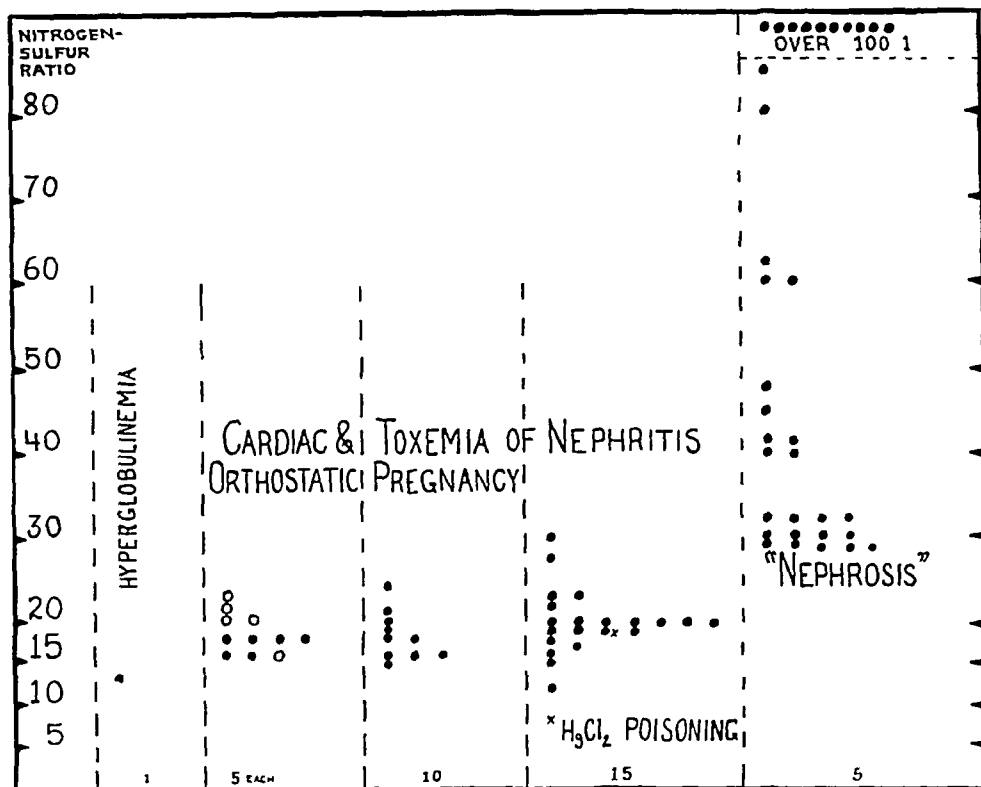
\* Five tenths gram of the dried coagulum or dialyzed protein was used for analysis. The values for the urinary protein were calculated for the twenty-four hour specimen.

In the accompanying chart are shown the results of all the analyses we have so far carried out in our preliminary survey of the problem. From this chart it is evident that patients with so-called nephrosis excrete a protein that is decidedly lower in sulfur content than the protein excreted by patients with other types of proteinuria. There appears to be a sharp dividing line between this disease and other conditions at a nitrogen-sulfur ratio of 30.1. If it is assumed that the proteinuria associated with congestive heart failure is due to increased oncotic pressure and transudation through the glomerulus into the urine, the findings for this group may be taken to represent values for serum protein. Similar considerations apply to so-called orthostatic albuminuria. The proteins excreted by patients with glomerulonephritis and with the toxemia of pregnancy are of the same order as far as the sulfur content is concerned.

Evidently only two types of patients excrete a protein of markedly different sulfur content, namely, patients with "nephrosis" and, possibly, persons with certain rare types of hyperproteinemia in which the excreted protein perhaps is related to the Bence-Jones protein.

Confirmatory evidence of these findings is available from other sources. Thus, Lang<sup>1</sup> demonstrated that in certain patients with renal disease there is a lowered cystine content of the serum and urinary protein. Schenck and his co-workers<sup>2</sup> also found lability in the amino-acid constitution of serum and organ protein. They demonstrated an inverse relationship between the cystine and the tryptophan content of various proteins, including the plasma protein<sup>3</sup>.

The body of evidence assembled by Lang and Schenck as to the lability of the body proteins in their amino-acid constitution is impres-



Variations in the sulfur content of urinary protein in various diseases associated with "albuminuria," expressed in terms of the nitrogen-sulfur ratio of the excreted protein. Each point represents the analysis of one specimen of urine. The small numerals at the bottom of each section of the chart indicate the number of cases studied. In the second section the results for cardiac proteinuria are indicated by solid dots and for orthostatic proteinuria by open circles.

1 Lang, K. Die chemische Zusammensetzung der Urineiweisskörper bei Albuminurien, *Arch f exper Path u Pharmacol* **171** 73, 1933.

2 Schenck, E. G., and Kunstmann, H. K. Ueber die Abhängigkeit des Baues der Proteine des Blutserums von den Stoffwechselvorgängen im Organismus. *Ztschr f physiol Chem* **215** 87, 1933.

3 Schenck, E. G., and Wollschitt, H. Untersuchungen über die Abhängigkeit des Baues der Gewebeeisweissstoffe von der Stoffwechselform des Organismus. Das Verhalten des Cystins und des Tyrosins, *Arch f exper Path u Pharmacol* **173** 269, 1933.



sive It includes diurnal variations,<sup>4</sup> individual variations, modification by roentgen therapy and other agents<sup>5</sup> and alterations in various diseases<sup>6</sup>

In the studies reported in this paper we have obtained one more evidence of such changes The method for determination of the nitrogen-sulfur ratio of excreted protein is sufficiently simple to make it of clinical use in the differentiation of the two types of proteinuria in renal disease

#### SUMMARY AND CONCLUSIONS

A simple method for determination of the nitrogen-sulfur ratio of urinary protein is described

In cases of congestive heart failure, orthostatic albuminuria and toxemia of pregnancy the nitrogen-sulfur ratio of urinary protein averages about 20 : 1

In cases of glomerulonephritis the sulfur content of the urinary protein is about the same as the sulfur content in the conditions just mentioned

The urinary protein excreted in cases of the nephrosis syndrome has a low sulfur content The nitrogen-sulfur ratio of this protein is above 30 : 1

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4 Lang, K Ueber die Tagesschwankung in dem Schwefel- und Tryptophangehalt der menschlichen Serumweissskörper, *Arch f exper Path u Pharmakol* **154** 342, 1930

5 Schenck, E G *Arch f exper Path u Pharmakol* **175** 401, 1934

6 Schenck, E G *Arch f exper Path u Pharmakol* **150** 160, 1930

# HIRSUTISM, HYPERTENSION AND OBESITY ASSOCIATED WITH CARCINOMA OF THE ADRENAL CORTEX

INDETERMINATE PITUITARY ADENOMA AND SELECTIVE CHANGES  
IN THE BETA CELLS (BASOPHILS) OF THE HYPOPHYSIS

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Hirsutism and obesity in association with tumor of the adrenal gland<sup>1</sup> were first noted almost two centuries ago. Sexual precocity was added to this syndrome in 1865<sup>2</sup>. Finally hypertension was noted in cases of this disorder in 1897<sup>3</sup>. The sexual changes were studied by Glynn<sup>4</sup> and Gallais,<sup>5</sup> who in 1912 independently reviewed the literature and emphasized the relationship of those changes to the age period in which changes in the adrenal cortex occur. 1. A tumor or hyperplasia of the adrenal cortex developing during the embryonic period may be associated with pseudohermaphroditism. 2. A like condition developing during early childhood may be associated with precocious obesity with or without sexual changes or (in the male) with the "infant Hercules" type. 3. The disorder when appearing during adolescence may cause adrenal virilism (otherwise called "genito-adrenal syndrome").

Glynn was not unmindful of the interrelationship between the pituitary gland and the adrenal cortex and quoted Cushing's work on the subject. In 1912 Cushing had described the "polyglandular syn-

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1 Cooke, William, 1756, cited by Linser, P. Ueber die Beziehungen zwischen Nebennieren und Körperwachsthum besonders Riesenwuchs, Beitr z klin Chir **37** 299, 1903.

2 Ogle, J W. Unusually Large Mass of Carcinomatous Deposit in One of the Suprarenal Capsules of a Child, Tr Path Soc London **16** 250, 1865.

3 Neusser, E. Die Erkrankungen der Nebennieren, in Nothnagel, C W. H. Specielle Pathologie und Therapie, Vienna, A Holder, 1897, vol 18, pt 3, p 71.

4 Glynn, E E. The Adrenal Cortex. Its Nests and Tumours, Quart J Med **5** 157, 1912.

5 Gallais, A. Le syndrome genito-surrenal, These de Paris, no 225, 1912.

drome,"<sup>6</sup> but he did not then suspect what he subsequently discovered, namely, that some of these syndromes were associated with a basophil adenoma of the anterior lobe of the pituitary gland. To this interesting condition he has drawn considerable attention,<sup>7</sup> and he has reported 14 cases with the results of autopsy. The patients presented a clinical picture practically indistinguishable from that of adrenal virilism. It is of interest that 8 of these 14 patients showed definite hyperplasia of the adrenal cortex, and 1 patient (Dr Anderson's) proved to have not only a basophilic adenoma of the pituitary but a "cortical adenoma or hypernephroma" of the adrenal gland.<sup>8</sup>

So far as we are aware,<sup>9</sup> this and Mathias'<sup>10</sup> case, to which we shall refer later, are the only recorded cases in which tumors have been found in the adrenal cortex and the anterior lobe of the pituitary gland of the same patient. We intend to record another case and to raise several questions which clinical, pathologic and hormonal studies have left unanswered.

#### REPORT OF A CASE

H. B., a girl aged 19, single, entered the third (New York University) medical division of the Bellevue Hospital for the second time on Dec. 27, 1933, complaining of progressive weakness, pain over the lumbar portion of the spine and lower part of the abdomen, increasing adiposity, edema of both feet and awkwardness of gait.

*Previous History*—The patient was an American of Irish descent, the youngest of six living children. The mother was 64 and well, the father had died at 56 of "pleurisy." The family history was irrelevant. During childhood the patient had measles and chickenpox, at 8 years she underwent a mastoidectomy on the right side, and at 16, one on the left. Menstruation began at 12 years, the cycle was regularly established at once, recurring every thirty days, the flow was moderate and painless, lasting seven days. The patient noted a yellowish vaginal discharge in February 1931, after sexual exposure, and in November 1932 a physician found gram-negative intracellular diplococci on a smear. From that time the menstrual flow increased to thirteen days each month but remained painless. Menstruation did not occur during March and April of 1933 or during the last month of the patient's life, there was no other history of amenorrhea.

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6 Cushing, H. *The Pituitary Body and Its Disorders*, Philadelphia, J. B. Lippincott Company, 1912.

7 Cushing, H. "Dyspituitarism." Twenty Years Later, with Special Consideration of Pituitary Adenomas, *Arch. Int. Med.* **51**: 487 (April) 1933.

8 Anderson, J. A Case of Polyglandular Syndrome with Adrenal Hypernephroma and Adenoma of the Pituitary Gland, *Glasgow M. J.* **83**: 178, 1915.

9 Since this report was submitted for publication, Lawrence and Zimmerman (Pituitary Basophilism. Report of a Case, *Arch. Int. Med.* **55**: 745 [May] 1935) have recorded another case of multiple adenomas of endocrine glands in a man aged 44 who exhibited the Cushing syndrome and marked skeletal demineralization. At necropsy adenomas were found in the adrenals, another was present in the parathyroid gland, and a basophilic cell new growth was found in the anterior lobe of the pituitary.

10 Mathias, E. Ueber Geschwulste der Nebennierenrinde mit morphogenetischen Wirkungen, *Virchows Arch. f. path. Anat.* **236**: 446, 1922.

The present illness began in April 1933, with pain in the small of the back, edema of both feet, sudden gain in weight from 119 to 135 pounds (54 to 61.2 Kg) and awkwardness in gait. These symptoms subsided during the next two months, and by June the patient was again able to put her shoes on easily. In September there was a recurrence of symptoms. Edema of the feet reappeared, the face became swollen and the abdomen swollen and tender. The weight rose from 135 to 150 pounds (61.2 to 68 Kg). The patient noted large dilated veins over her breasts, thighs and abdomen. In October, she began to shave her face because of excess hair.

In November, pain in the lower portion of the abdomen became severe enough to cause the patient to come to the hospital, where she was admitted to the gynecological service. At that time she weighed 158 pounds (71.7 Kg). Large striae were noted on the abdomen and thighs, and dilated veins were observed on the chest and abdomen. There was tenderness in both lower quadrants of the abdomen, and a vaginal discharge containing gram-negative intracellular diplococci was present. It is important to note that on admission, November 13, the blood pressure was 124 systolic and 90 diastolic, and on November 18 it was 148 systolic and 92 diastolic. Urinalysis revealed albumin (1 plus), from 8 to 10 white blood cells per high power field and urobilinogen in a 1:5 dilution. The Wassermann test was negative.

The patient was transferred to the medical service, where on November 24 the basal metabolic rate was found to be  $-7$  per cent. The general condition improved, and on November 28 she was discharged to the endocrinology clinic, but she was sent back for hospitalization one month later. On this second admission, there were added to her complaints a cough productive of blood-streaked sputum and the appearance of purpuric areas in the skin.

*Examination and Course*—The patient presented a rather striking appearance on examination (fig 1). She was of hypersthenic habitus and appeared to be older than her age, her weight was 156½ pounds (71 Kg) and her height 65 inches (1.65 meter). Her body had a peculiar pungent "sweaty" odor. "Pig face" best describes the appearance of the countenance, and the large chest and abdomen seemed out of proportion to the wasted upper and lower extremities. The skin was dull grayish brown, dry and coarse and bore purpuric patches varying from 5 to 25 mm in diameter over the anterior surfaces of both thighs and extensor surfaces of both forearms. The patient did not present a plethoric appearance. Conspicuous were the long, broad symmetrical striae over the abdomen and upper portion of the thighs. These were reddish purple and were traversed here and there by dilated, dark blue tortuous veins as well as by fine, straight, bright red capillaries. Smaller striae were present over both mammae and over the proximal third of both arms at their outer aspects. Hypertrichosis was noted over the face, chin, upper lip and extensor surfaces of the legs and forearms. The hair of the head was long and dry. There was a female distribution of pubic hair. Fine dry brownish papules were distributed over the dorsa of the fingers and flexor surfaces of both wrists as well as over the outer aspects of both arms. Many comedones were seen on her greasy face. The eyes were almond-shaped, the pupils were normal. In the fundi were a few small spindle-shaped hemorrhagic areas, the arterioles were tortuous and of normal caliber. The venules looked normal and were not compressed. There was no exudate, and the margins of the disks were clear. The visual fields were normal. Both external auditory canals contained slight amounts of thick yellowish purulent discharge. Conspicuous interspaces separated the teeth, though all the molars were present.

The neck was short, and the thyroid was not palpable. Over the entire anterior surface of the chest and over the upper portion of the abdomen was noted a network of pale blue, dilated, tortuous veins. Except for the striae the mammae were normal. The lungs were clear except for dulness and diminished breathing over the lower lobe of the right lung. The heart was normal.

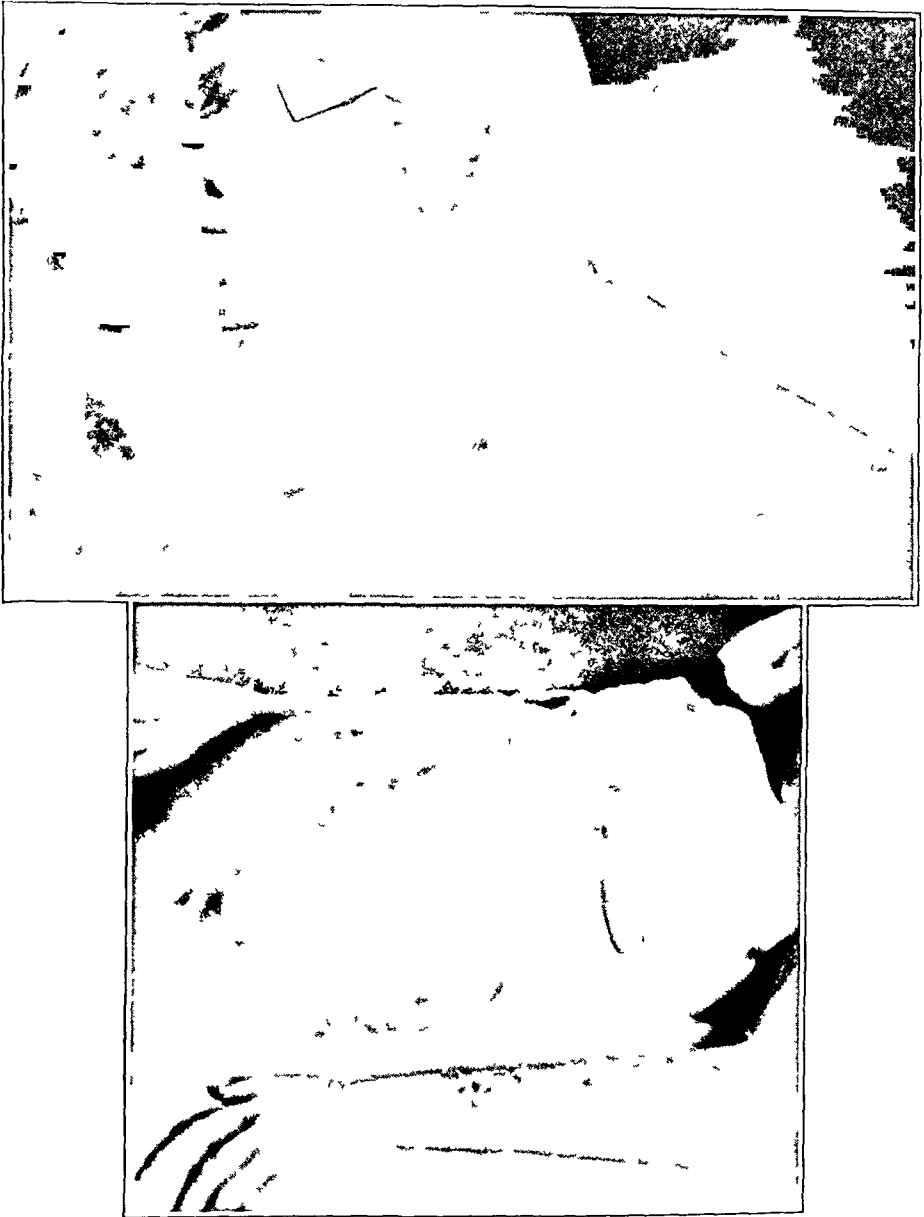


Fig 1—Photographs of the patient, showing hypertrichosis on the face and striae atrophicae in the axillae and over the breasts, abdomen and upper portion of the thighs. Note also the severe purpuric eruption on the forearm.

The abdomen was protuberant and bulged in the flanks. Signs of free fluid in the abdominal cavity were equivocal. The edge of the liver was palpable 6 cm below the right costal margin and could be traced across the abdomen to a similar distance below the left costal margin, its surface was smooth. There

was considerable tenderness on light pressure over the entire abdominal wall. There was soft pitting edema (4 plus) of the dorsa of both feet and legs. The spinal column showed no deformity. Vaginal examination gave negative results except for vaginal discharge. The clitoris was of normal size. Neurologic examination gave negative results. Mentally the patient was sluggish, often non-comprehending, though her memory was fairly good both for recent and remote past events.

On admission the body temperature was 98 F. The urine was normal except for slight proteinuria. The red blood cells numbered 3,100,000, the hemoglobin content was 60 per cent, or 7.8 Gm (Dare), the white blood cell count showed 16,900 leukocytes with 58 per cent polymorphonuclears, 16 per cent metamyelocytes II, 8 per cent metamyelocytes I, 14 per cent lymphocytes, 2 per cent eosinophils and 2 per cent monocytes. The Wassermann reaction of the blood was negative.

Despite progressive asthenia, the patient felt comfortable during the first four weeks of her stay in the hospital. She became slovenly in her habits and lost all modesty. No changes in voice were noted. The weight gradually fell from 156 to 150 pounds (70.8 to 68 Kg), and edema of the feet and legs disappeared. The temperature fluctuated between 98 and 101 F. Readings of the blood pressure taken frequently varied from 180 to 168 mm of mercury systolic and from 138 to 125 diastolic.

Roentgenologic studies were reported as showing several small and large circumscribed areas of increased density in both pulmonary fields suggesting the presence of metastatic neoplasm. The bones of the skull showed no changes, the sella turcica was normal, measuring 10 mm in anteroposterior diameter and 6 mm in depth, and the clinoids were well formed and preserved. A slight degree of rarefaction was noted in the thoracic and lumbar portions of the spine. Roentgenograms of the long bones and of the heart showed no abnormalities.

On January 4 the Aschheim-Zondek test was negative.

On January 9 the basal metabolic rate was + 3 per cent.

Several urinalyses revealed proteinuria, the protein content varying from 1 to 4 plus, the specific gravity varied from 1.012 to 1.015, occasionally there were 1 or 2 white blood cells and as many red blood cells per high power field. No reducing or acetone bodies were detected. The results of determinations of urobilinogen were as follows: on January 9 a positive reaction was obtained with a 1:80 dilution, on January 10, with a 1:320 dilution, on January 16, with a 1:80 dilution, and on January 26, with a 1:80 dilution.

The dextrose tolerance test, on January 20, gave the following results: during fasting, 81.3 mg, thirty minutes after ingestion of 100 Gm of dextrose, 121.2 mg, at the end of sixty minutes, 166.7 mg, at the end of one hundred and twenty minutes, 173.9 mg, and at the end of one hundred and eighty minutes, 162.6 mg, per hundred cubic centimeters of blood.

Chemical studies of the blood made on January 22 showed nonprotein nitrogen, 30 mg per hundred cubic centimeters, sugar, 84 mg, and serum calcium, 11.4 mg. The icteric index was 15, the van den Bergh test gave a direct immediate positive and an indirect positive (qualitative) reaction.

During the last two weeks of the patient's life, Dr. Robert T. Frank of the Mount Sinai Hospital made hormonal studies on her blood and urine and reported the following results: "The urine contained as much as 5,000 mouse units of estrogenic substance per liter, a quantity far exceeding that found in pregnancy. As a control, however, the Friedman test was performed on two rabbits with the same urine, but a negative reaction was obtained. There was no excess of the

gonadotropic factor in the urine. The venous blood contained 1 mouse unit to 40 cc, which is a normal value. In other words, as far as the humoral condition was concerned, the findings were essentially normal except for the tremendous over-excretion of estrogenic substance in the urine." No analysis was made for androgenic substance.

Because new purpuric areas were repeatedly noted in the skin and a Rumpel-Leeds test (with pressure of 150 mm of mercury) resulted in the appearance of myriads of purpuric spots over the dorsal aspect of the wrist, Dr Connery of the hematologic service was asked to see the patient. On January 22, nine days before the patient's death, he reported the following results of tests on the blood: red blood cells, 3,310,000, hemoglobin (Klett and Newcomer), 54 per cent (97 Gm), color index, 0.82, mean corpuscular hemoglobin, 27 micromicrograms (the normal amount is from 27 to 32 micromicrograms), mean corpuscular volume, 104 cu mm (the normal amount is from 80 to 94 cu mm), platelets, 157,000 per cu mm, bleeding time (Duke) six and a half minutes, coagulation time (Lee and White), eight and a half minutes, nine minutes, twelve minutes, ten minutes and ten and a half minutes, respectively, in five tests, fragility of the red blood cells (Sanford), from 0.48 to 0.32 per cent (control, from 0.44 to 0.32 per cent), erythrocyte sedimentation rate (Plass and Rourke), 87.5 per cent of total possible settling in one hour (upper limit of normal, 65 per cent), serum bilirubin, 17 mg per hundred cubic centimeters.

The results of the differential count were reported by Dr Connery as follows: 62 per cent polymorphonuclears, 20 per cent metamyelocytes II, 5 per cent metamyelocytes I, 1 per cent myelocytes and 10 per cent lymphocytes. The smear also showed 3 normoblasts per hundred white blood cells and moderate qualitative regenerative changes in the red blood cells. There were 66 per cent reticulocytes.

Dr Connery expressed the opinion that the patient presented the following evidence of a hemolytic factor: (1) anemia with striking qualitative regenerative changes, (2) the presence of fragmented red cells and of many nucleated red cells, (3) an increased percentage of reticulocytes, (4) leukocytosis with a striking shift to the left, (5) an increased amount of urobilinogen in the urine, and (6) pertinently increased fragility of the red cells.

On January 25, the patient's temperature rose to 103.4 F and a large abscess was noted on the upper portion of the left thigh, from which hemolytic streptococci were recovered in pure culture. Later that day she became comatose, and a lumbar puncture was made. The spinal fluid escaped under normal pressure, it was clear and colorless and contained a normal amount of reducing bodies, no globulin and 14 lymphocytes per cubic millimeter.

The patient went rapidly downhill. She became incontinent of urine and feces, the striae over the lower portion of the abdomen began to suppurate, her temperature remained at 103 F and she died on January 31.

*Autopsy*—Autopsy was performed two hours after death.

*Macroscopic Examination* The results of external examination conformed to the aforementioned observations. Many of the striae were found to be ulcerated, some showing raised bullae filled with serous or purulent fluid. On the inner aspect of the left gluteal fold and extending forward to the region of the perineum was an area of diffuse inflammatory edema about 10 by 12 cm, perforated by many irregular ulcerations of varying size. On section the increase in depot fat was noted everywhere.

On dissection of the abdominal viscera, the right kidney was found displaced downward by a large tumor situated at its upper pole (fig 2). Posteriorly the

tumor completely compressed the inferior vena cava and was firmly attached to the right lobe of the liver. It measured 15 by 18 by 16 cm exclusive of the hepatic portion. The tumor was lobulated and encapsulated for the most part. The right kidney was intact and normal except for its displacement. In the tumor no trace of the right adrenal could be found.

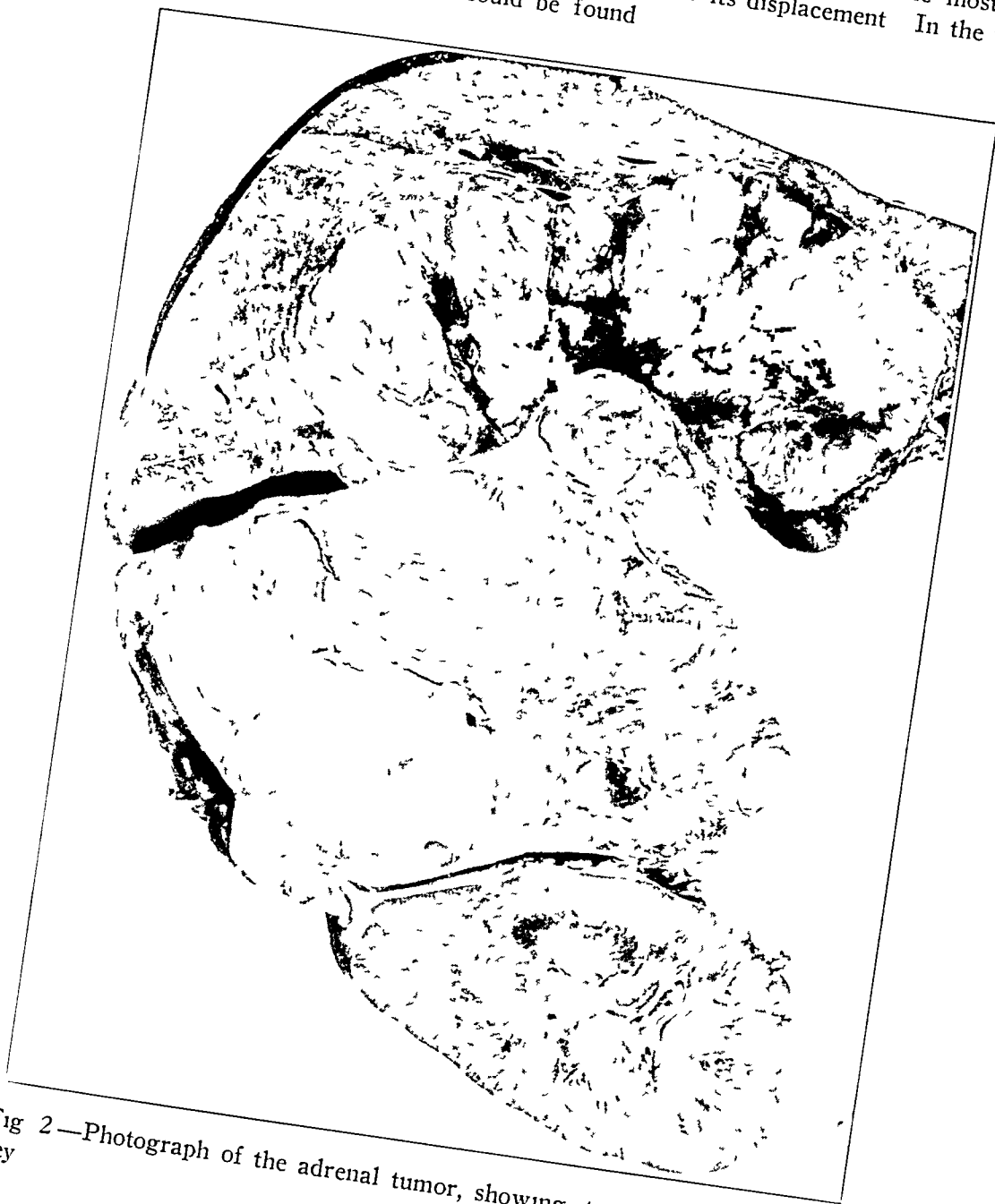


Fig 2—Photograph of the adrenal tumor, showing its relation to the liver and kidney

Cut section of the tumor<sup>11</sup> showed an irregular lobulated appearance. Some areas were butter-yellow, others were necrotic, and others were the seat of recent

<sup>11</sup> Several pieces of tumor were extracted for a pressor substance by Dr Goettler, of the chemistry laboratory of the Bellevue Hospital, after the method

(Footnote continued on next page)



and old hemorrhage. The apparently best preserved portions of the tumor had a distinctly grayish-pink hue and were fleshy and fairly firm. Section of the liver and tumor in the frontal plane showed deep invasion of the right lobe, with pressure atrophy of the adjacent parenchyma and a few scattered metastases beyond. Thrombi were occasionally found in the hepatic veins and were readily extruded. The intact parenchyma of the liver showed the markings of chronic passive congestion. The structures of the hilus and gallbladder were normal. Dissection of the inferior vena cava from its opening in the right auricle showed it to be filled with soft tumor deposits.

There was no evidence of thymic tissue in the precordial and superior mediastinal fat.

The lungs contained numerous metastatic nodules in otherwise intact parenchyma.

The heart was not enlarged. The left ventricle was contracted, its walls were of normal thickness. The endocardial structures were intact. The aorta was elastic and of narrow caliber. Its intima was smooth and free from visible atheroma.

The left adrenal was small and wrinkled. On section the cortex seemed narrow and the medulla poorly defined, there was no autolysis.

The ovaries were small and firm and cut with increased resistance. No cysts or traces of lutein tissue were seen.

The bones of the skull, ribs and sternum were normal.

The pancreas, thyroid and parathyroids showed no changes.

All the other organs showed no macroscopic changes.

**Pituitary Body.** This was removed with the encasing sella turcica. After it was dissected no macroscopic changes were seen. The gland was not enlarged. It measured 13 mm in anteroposterior diameter, 14 mm in the lateral dimension and 6 mm vertically. A sagittal section was cut through the gland, including the stalk. No abnormality was seen on either cut surface.

**Microscopic Examination.** Sections of the tumor (fig 3) revealed a new growth consistent with the picture of carcinoma arising in the cortex of the adrenal. The metastases showed the most consistent morphology and the best preserved cells. Degenerative changes were numerous in all the portions studied. Tissue fixed in absolute alcohol and stained by Best's method showed no glycogen in the sections taken.

The examination of the vascular tree revealed no significant changes indicative of preexisting hypertension except focal arteriosclerosis in the kidney and some focal thickening of the basement membrane in an occasional glomerulus. The tubules showed widespread degenerative changes, many of them contained red cell casts.

There was evidence of hematopoiesis in the spleen. There was also slight increase in reticulum strands in the lymphoid follicles.

Section of the thyroid showed it to be in a resting state approaching hypoplasia.

Twenty-eight sections of each ovary (fig 4) at depths of 50 microns were prepared. One oocyte was seen in each series, one fairly well preserved and one

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given by Hick (A Suprarenalin-Producing Pheochromocytoma of the Suprarenal Gland, Arch Path **15** 665 [May] 1933). Professor Wallace, of the department of pharmacology, who used the same material in testing a dog, found no elevation of blood pressure. Dr Robert T. Frank, of the Mount Sinai Hospital, found each gram of the tumor tissue to contain twice the amount of estrogenic substance that could be recovered from a gram of the normal spleen from the same patient used as control.



Fig 3—Photomicrograph of a section through one of the tumor nodules, showing the compact arrangement of the cells, chiefly in cords. Marked variation in size and shape and staining affinity can also be seen.

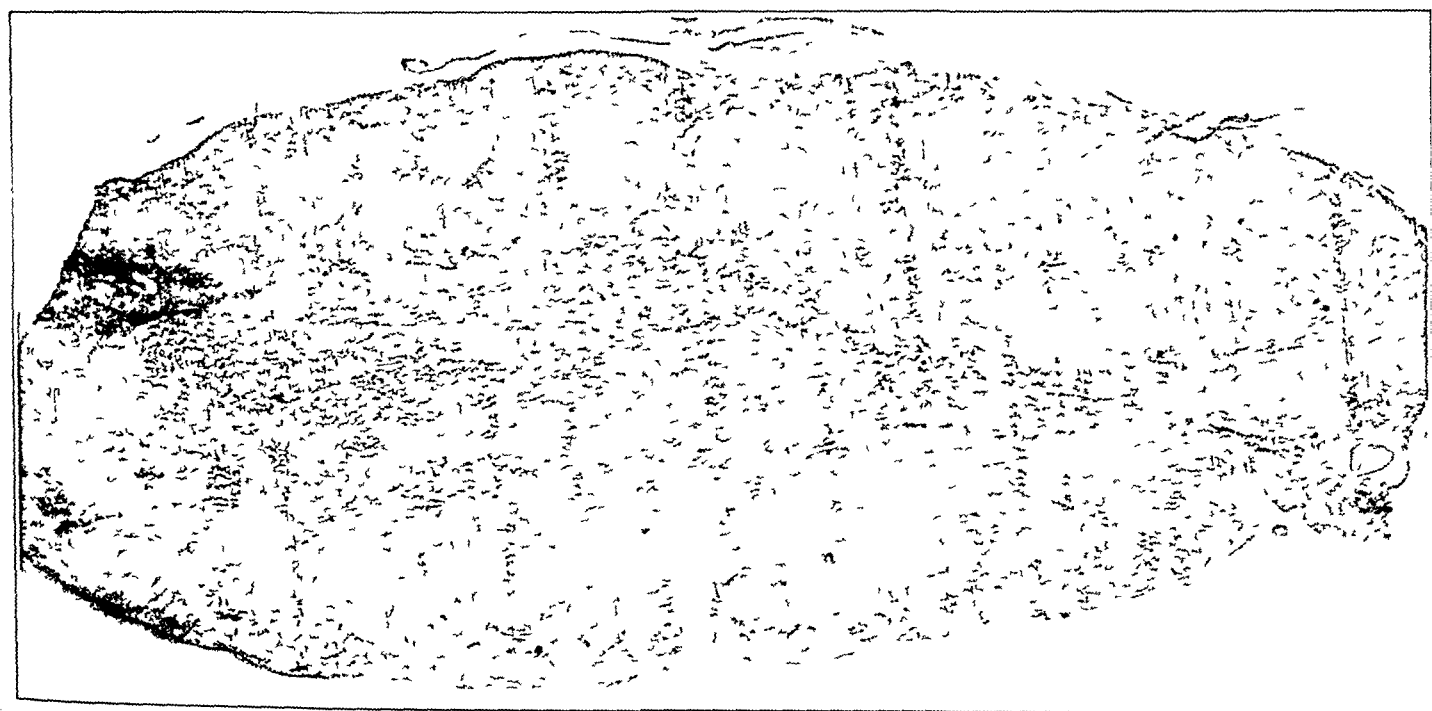


Fig 4—Photomicrograph (low power magnification) of a section of the right ovary made in the longest dimension. One maturing follicle can be seen in the lower right corner. Elsewhere the ovary shows marked fibrosis with atresia of the follicles.

undergoing degeneration Both ovaries were relatively bloodless and showed an unusual amount of progressive atresia of the follicles in all stages In some fields scarcely any primordial follicles were seen, and in others as many as eight were present these too were in various stages of atresia There were a few surface tags of adhesions and inclusion of peritoneum

Sections of the endometrium showed atrophy of the glands, marked edema and swelling of the outer two thirds of the mucosa

Sections of all parts of the pancreas showed well preserved acinar tissue The islands of Langerhans seemed normal except for focal hemorrhage in an occasional islet

The left adrenal was cut into five blocks, and many sections from each block showed no chromaffinic granules The medulla appeared scanty and was barely distinguishable from the cortex, the cortex was narrow and the zona reticularis atrophic The central vein and its branches showed irregular hypertrophy of its muscular wall

The pineal body exhibited no noteworthy changes

The sections of the other organs with the exception of the pituitary gland revealed no significant alterations

**Pituitary Gland** Sagittally cut serial sections (5 microns thick) were prepared of the halves of the gland after the tissue had been fixed in Zenker's fluid and embedded in paraffin About thirty-five sections were lost in preparation

In one block a miliary oval circumscribed nodule (fig 5) was found in the inferior portion of the anterior lobe just within the capsule It measured 1 mm by 850 microns and appeared to have compressed the surrounding tissue

The first impression on seeing sections stained with Delafield's hematoxylin, a dilute Giemsa solution or iron hematoxylin and eosin was that the nodule represented a basophil adenoma

However, when special cytoplasmic stains<sup>12</sup> were employed, and particularly after sections had been mordanted in 3 per cent potassium di-chromate for several days, it became clear that most of the cells in the nodule contained no chromophilic granules

The vast majority of cells (fig 6) showed scanty ill defined cytoplasm without granules and were loosely arranged around dilated capillaries and in discrete clumps presenting no definite pattern There were a few eosinophilic cells and recognizable basophils at the periphery and rarely in the central portion of the tumor

While the majority of cells tended to take a feeble bluish-purple hue with hematoxylin, ordinary immersion in a 1 per cent aqueous solution of eosin gave them a reddish tint The nuclei of many of the ill defined cells showed striking vesicular degenerative changes, and this feature was common to the basophils outside of the nodule This was considered to constitute possible evidence of kinship At times the nuclei were pyknotic and fuchsinophilic These observations will be detailed later

The capsule of the nodule (fig 6) appeared to be composed of preexisting reticular and collagenous fibers (perhaps brought together by pressure atrophy of

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12 The following technics and stains were used Severinghaus' method, Bailey's method which employs acid violet and Altmann's aniline fuchsin, Mallory's aniline blue, the Weigert method employing gentian violet, iron hematoxylin, Heidenhain's azocarmine, Giemsa stains, and a new method introduced by Soos and Csizsek (*Die elektive Färbung der basophilen Granulen des Hirnanhangs*, *Endokrinologie* 10 410, 1932)

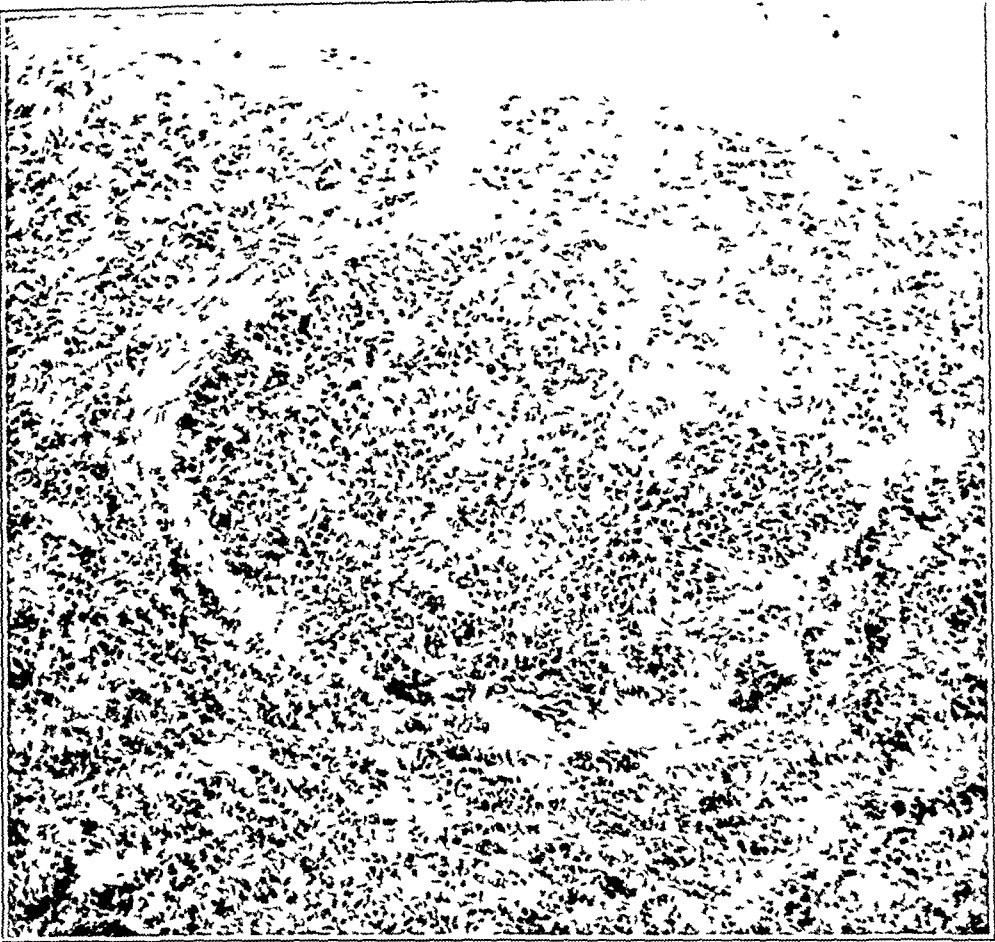


Fig 5—Photomicrograph (low power magnification) of a section through the adenomatous nodule in the anterior lobe of the hypophysis. Note the compression of the surrounding tissue, the poorly defined capsule and the irregular arrangement of the cells within the nodule.

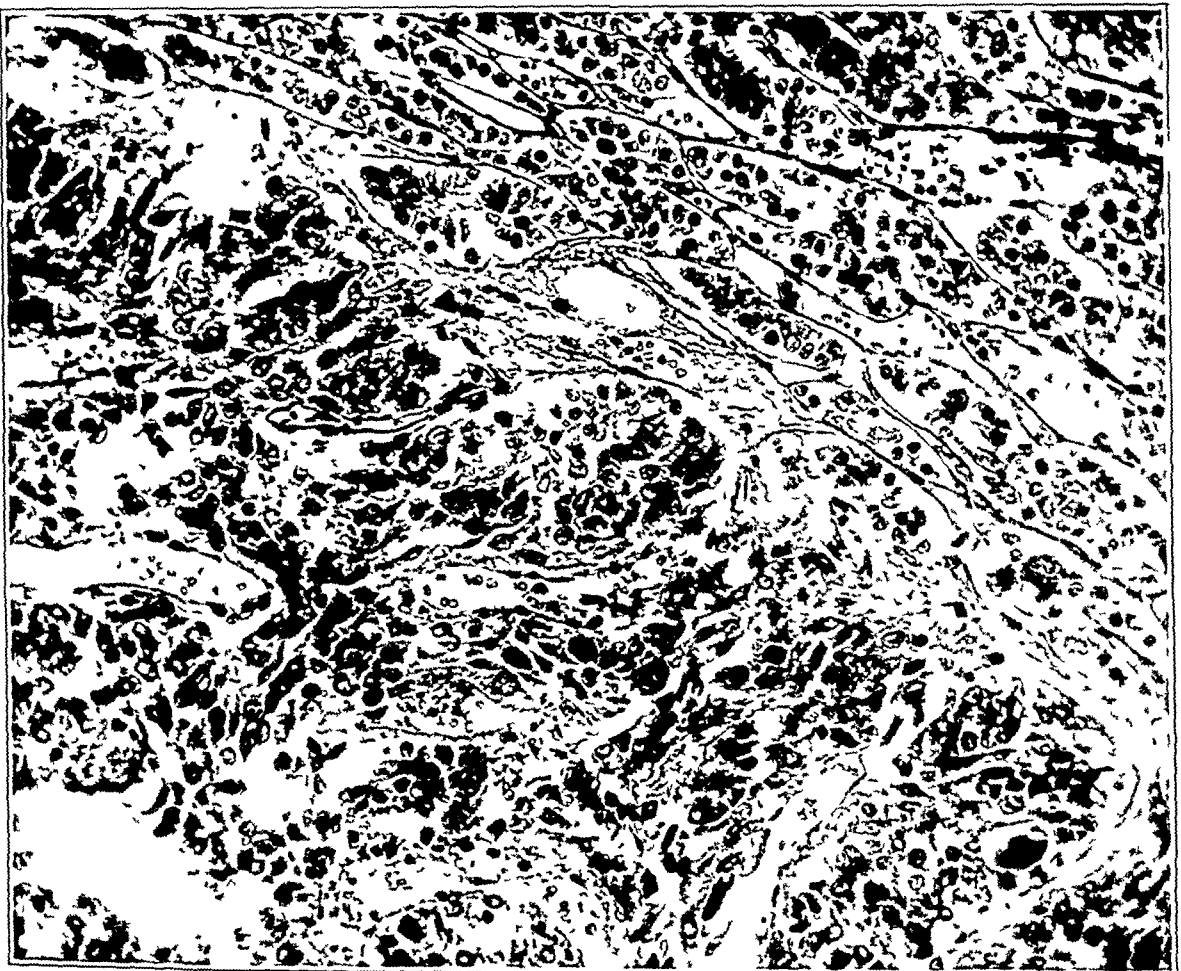


Fig 6—Photomicrograph of a section through the edge of the nodule shown in figure 5 (stained by the method of Foot and Foot for reticulum). Note the absence of reticulum fibers within the nodule, contrast the disorderly arrangement of the cells within the nodule with that of the surrounding tissue.

the intervening parenchyma) Externally the fibers were continuous with the stroma of the adjacent tissue Little or no stroma was demonstrable in the tumor, this formed a sharp contrast to the remainder of the pars anterior

Outside the nodule (fig 7) the eosinophils were uniform in size, and their granules were brilliantly clear and easily demonstrated A few degenerated ones were seen within the adenomatous nodule Some transitional forms were encountered in all fields The chief cells were not noticeably altered

The basophils were conspicuously altered (fig 7) While the size and affinity of the cytoplasm for the appropriate dyes indicated that they were beta cells, their granules were not demonstrated as such<sup>13</sup>

Reference has been made to nuclear changes in many of the cells of the adenomatous nodule Similar alterations were exhibited by the beta cells throughout the anterior lobe Their nuclei wherever studied were enlarged In some the swelling had increased their nuclear outline until it reached to just within the periphery of the cytoplasm In others several clear vesicles were seen in a single nucleus, outlined by fine chromatinic lines, filling and giving the nucleus a lobulated appearance

Elsewhere the nuclear membrane appeared to be dissolving and merging imperceptibly with the cytoplasm In other cells small vesicles<sup>14</sup> (vacuoles) could be seen in what appeared to be a process of extrusion through the nuclear membrane Amitotic division was encountered also, and multinucleated forms (of basophils) were found inside and outside of the nodule Not infrequently a pyknotic nucleus was seen, and in sections stained by the method of Severinghaus they were fuchsinophilic

So-called *entgranulierten* (degranulated) cells were occasionally found both within and without the nodule They were approximately the same size as the basophils elsewhere

Sections of the hypothalamic region<sup>15</sup> and of other portions of the brain showed no pathologic changes

*Final Pathologic Diagnosis*—The final diagnosis was carcinoma of the right adrenal gland with metastases to the liver, inferior vena cava and lungs, indeterminate adenoma of the pars anterior of the pituitary gland, selective vesicular degeneration of the beta cells of the hypophysis, atrophy of the ovaries and endometrium, slight atrophy of the left adrenal gland, slight hypoplasia of the thyroid gland, hypertrichosis, obesity, sepsis from striae infected with *Streptococcus haemolyticus*

#### COMMENT

This case presents once more the opportunity to point out, as others before us have done, the important clinical observation that the syndrome here described is not specific for any single endocrine disturbance The recent literature contains ample evidence that the same clinical picture may be associated with a basophil adenoma of the pituitary, hyperplasia or a tumor of the adrenal cortex, a tumor of the thymus or an arrhenoblastoma of the ovary

13 Three hundred cells counted showed no cytoplasmic granules This is interesting since Bailey and Davidoff have found that in material fixed in Zenker's fluid the sublimate may produce artificial granulation simulating beta granules

14 The vesicles exhibited no chromatism with any of the stains employed

15 Dr Lewis Stevenson examined the brain and reported the results of his examination

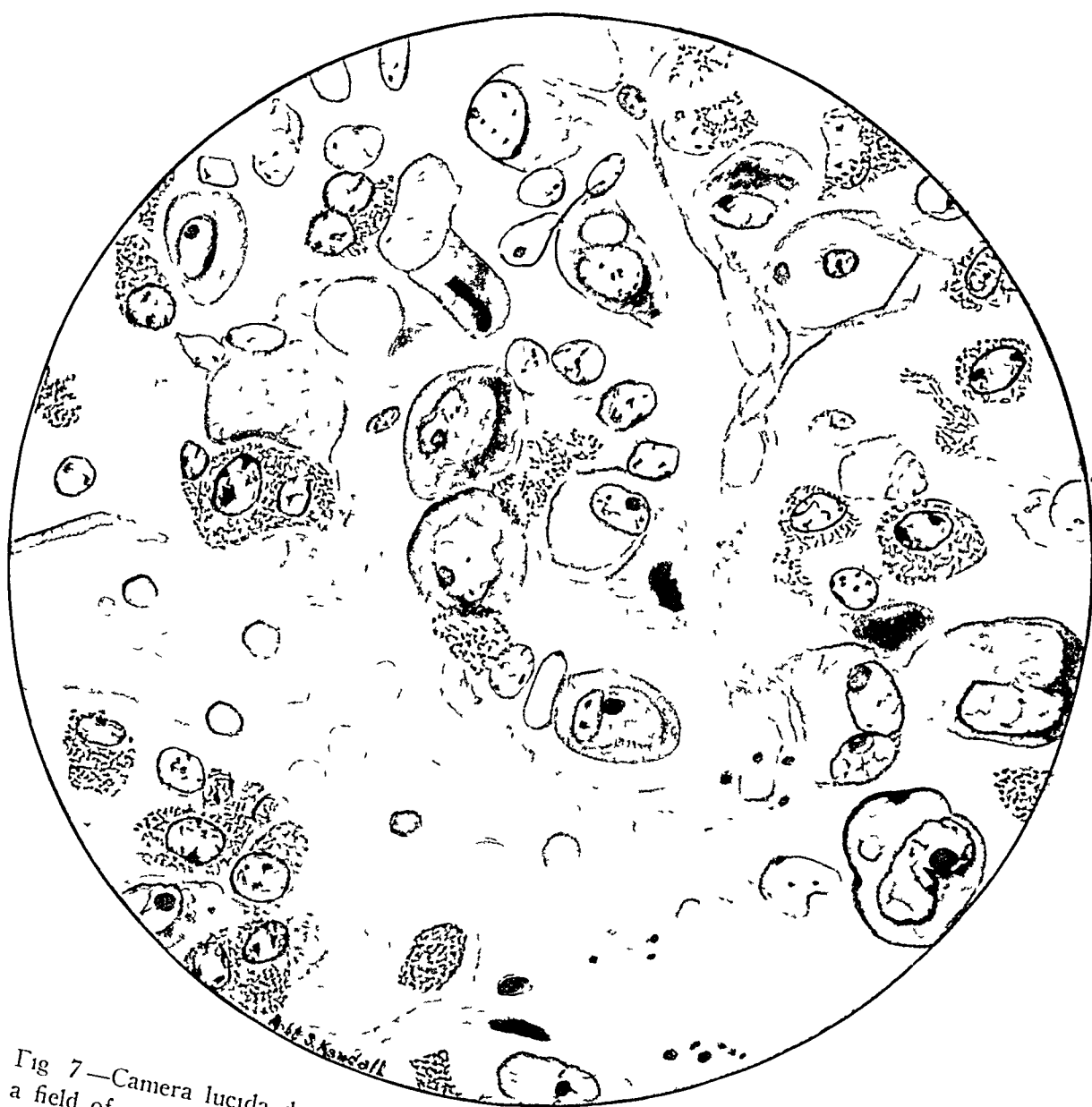


Fig 7—Camera lucida drawing (Leitz oil immersion lens 1/12, ocular 10 $\times$ ) of a field of a section of the pituitary gland, illustrating the loss of cytoplasmic granules in the beta cells, the marked vesicular swelling of the nuclei and the presence of large hyaloplasmic vesicles. Some basophils exhibit pyknotic nuclei which are fuchsinophilic. The section was stained by the Severinghaus modification of Masson's trichrome stain.



The relationship of the adrenal neoplasm to the clinical manifestations seems clear. The observations on the pituitary gland raise several questions, which we shall attempt to answer.

The nature of the tumor nodule in the pars anterior is difficult to determine. It partially satisfies the criteria given by Kraus<sup>16</sup> in his study of adenoma of the anterior lobe of the pituitary. It possesses a capsule and compresses the adjacent tissue. However, it is not composed of cells of one type. At its periphery are found various intact cells normal to the anterior lobe. The absence of reticular stroma within the nodule and the ill defined cell clumps which compose it indicate a focus of cells growing autonomously.

Unfortunately, these cells exhibit degenerative changes which mask their true nature. It seems best in view of inconclusive identification to call the nodule an indeterminate adenoma.

To determine whether or not the adenoma is merely coincidental, one should know the incidence of such tumors in the general population free from endocrine changes. Such data are not as yet available on a statistical basis. In a recent bulletin of the Mayo Clinic, Costello<sup>17</sup> is said to have studied 1,000 pituitary glands obtained at random in post-mortem examinations of patients with no history of endocrine abnormality. Each hypophysis was sectioned serially at intervals of 1 mm. Approximately 20 per cent contained adenomas, and one fifth of these were basophil. The age and sex distribution and relation to pregnancy, however, are not given, and evaluation of Costello's figures must await full report.

The recent report of Close<sup>18</sup> is pertinent in this regard. He studied the incidence of pituitary adenomas in about 200 patients examined at necropsy and found such tumors in about 10 per cent of the glands, although they were not all serially sectioned. Without indicating the incidence according to age he noted that most of the adenomas occurred in persons over 45 who had a benign or malignant neoplasm elsewhere. He then studied 125 of these pituitaries in serial sections, 75 from patients with a true neoplasm elsewhere in the body, and 50 from persons over 45 in whom in a routine autopsy no other tumor was found. The incidence of adenoma of the pituitary gland is given by him as

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16 Kraus, E. J. Die Beziehungen der Zellen des Vorderlappens des menschlichen Hypophyse zueinander unter normalen Verhältnissen und in Tumoren, *Beitr z path Anat u z allg Path* **58** 159, 1914.

17 Costello, R. T., cited by Kepler, E. J., Kennedy, R. L. J., Davis, A. C., Walters, W., and Wilder, R. M. Suprarenocortical Syndrome and Pituitary Basophilism. Presentation of Three New Cases, *Proc Staff Meet, Mayo Clin* **9** 169, 1934.

18 Close, H. G. *Lancet* **1** 732 (April 7) 1934.



follows (1) 10 per cent in all cases, (2) 44 per cent in cases of carcinoma, (3) over 50 per cent in cases of certain types of carcinoma (pancreatic, rectal and bronchial) and in cases of adenoma of the prostate. Thirty-seven, or approximately 95 per cent, of the adenomas were of chromophobe and none of the basophil type. Close's studies have led him to suggest a hormonal basis for the development of some pituitary adenomas in patients with carcinoma. It will be interesting if other cases of adrenocortical carcinoma associated with pituitary adenoma can be explained on the same basis. As Close pointed out, the development of multiple tumors may be merely a part of the constitutional tendency to tumor formation.

To obtain some idea of the age relationship of pituitary adenomas in persons free from endocrine disturbances, we have analyzed the data published by Erdheim and Stumme<sup>19</sup> and Kraus,<sup>16</sup> who studied their material in serial histologic sections. The former found adenomas or foci of adenomatoid hyperplasia in 12 of 119 patients. Kraus found adenomas in 25 of 300 pituitaries. There is an incidence in this series comparable to that reported by Erdheim. An analysis of the age incidence in the combined reports (we have deducted 3 cases because of associated endocrine disorders) reveals the following distribution:

From 1 to 10 years	1 case
From 11 to 20 years	1 case
From 21 to 30 years	4 cases
From 31 to 40 years	4 cases
From 41 to 50 years	10 cases
From 51 to 60 years	7 cases
From 61 to 70 years	1 case
From 71 to 80 years	2 cases
From 81 to 90 years	2 cases
Age unknown	2 cases
Total	34 cases

It is interesting that in 25, or 73 per cent, of these 34 cases the patient was between the third and the seventh decade. The inference is plain then that the nodules<sup>20</sup> in the case here reported may not be dismissed as being merely coincidental.

No light can be thrown on the nature of the nuclear changes described for the cells of the pituitary adenoma and the beta cells

19 Erdheim, J, and Stumme, E. Ueber die Schwangerschaftsveränderung der Hypophyse, Beitr z path Anat u z allg Path **46** 1, 1909

20 We are aware of the impossibility of assigning a physiologic or patho-physiologic role to the nodules, especially since the literature contains reports (some cited here) of cases of similar tumors without endocrine disturbance.

outside. Inability to demonstrate the granules of these cells alone is of little significance because of possible postmortem change. However, this observation and the severe nuclear regressive changes together seem to indicate a selective pathologic process.<sup>21</sup> The integrity of the chief cells and the eosinophils serves to emphasize the selectivity of the process.

Hypophyses<sup>22</sup> from patients dying of other types of malignant metastasizing newgrowths, sepsis or trauma and the hypophysis of another patient with an adrenal tumor have been examined by us and have failed to show similar cellular changes. The pituitary-adrenal relationship may be invoked as possibly encompassing these selective changes in some peculiar and inconsistent manner. Proof awaits additional cases of similar involvement and particular search of the hypophysis for similar lesions.

Are the changes in the pituitary gland evidence of a reciprocal adrenal-pituitary relationship? To consider that they may be seems reasonable, yet little evidence is available to establish this point.

Numerous observations show the influence of the pituitary gland on the adrenal cortex, but surprisingly few well controlled studies bear on a converse influence. Smith<sup>23</sup> showed that the adrenal glands of hypophysectomized rats shrink rapidly (in six days) to one-half the size of the adrenal glands of controls and that this shrinkage is almost entirely due to retrogression of the cortex. He showed further that atrophy of the adrenal cortex does not occur when only the posterior lobe of the pituitary is ablated and, lastly, that the atrophic glands of the hypophysectomized rats can be promptly restored to normal or near normal by daily homeotransplants of anterior lobe of the pituitary.

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21 Since this report was submitted A. C. Crooke (J. Path. & Bact. **41** 339, 1935) has reported the occurrence of selective hyaline changes with loss of granules in the cytoplasm of the basophil cells of the pituitary gland in 12 examples of the clinical syndrome exhibited by our patient. His cases include patients with basophil adenoma of the pituitary gland, neoplasm of the thymus and neoplasm or hyperplasia of the adrenal cortex. In a later personal communication and after examining a section of the pituitary gland of our patient Dr. Crooke concluded that our patient exhibited the same cytoplasmic change in a final stage. (These changes are illustrated in figure 8 of the aforementioned article by Crooke.) He added (Feb. 7, 1936) that he had found this hyaline change in 29 cases of so-called basophilism associated with adenoma in the pituitary gland, neoplasm of the adrenal cortex or carcinoma of the thymus.

22 Somewhat similar changes have been claimed by Kraus<sup>27</sup> to occur in the basophils in the hypophyses of patients dying of Addison's disease—a clinical syndrome and adrenal disorder unrelated to the one under discussion.

23 Smith, P. E. Hypophysectomy and Replacement Therapy in Rat, *Am. J. Anat.* **45** 205, 1930.

Putnam, Teel and Benedict <sup>24</sup> recently reported cortical adenomatosis of the adrenal gland in 1 of 2 dogs rendered acromegalic by the intra-peritoneal injection of anterior pituitary extract Thompson and Troppoli, <sup>25</sup> working in Cushing's laboratory, were believed by him to have demonstrated experimentally in rats that pituitary gonadotropic extract serves as a stimulant of the adrenal cortex Collip, Anderson and Thomson <sup>26</sup> claimed to have isolated chemically from the anterior lobe of the pituitary an "adrenotropic factor" which when administered to 125 hypophysectomized rats caused an increase of from 50 to 300 per cent in the weight of their adrenals

Supplementing these experimental reports are a number of clinical observations which demonstrate the interrelationship It is well known, for example, that in anencephalic fetuses in which the anterior portion of the brain is involved the adrenal cortex is aplastic or absent Mention has been made of the cases of "pituitary basophilism" described by Cushing, <sup>7</sup> in the majority of which there was definite hyperplasia of adrenal cortex

The foregoing citations illustrate the influence of the pituitary gland on the adrenals The direct effect of the adrenals on the pituitary has not as yet been definitely determined Clinical sources for such a study have been limited practically to cases of Addison's disease Kraus <sup>27</sup> Kiyono <sup>28</sup> and Berblinger <sup>29</sup> have described quantitative and qualitative changes in the basophilic cells of the pituitary in such cases These cells diminish in number and show regressive changes in their nuclei and cytoplasm The chief cells increase at the expense of the basophils As to the eosinophils, there is no agreement in the results of observations

The experimental studies on the adrenal-pituitary relationship have recently been reviewed by Houssay, <sup>30</sup> who found no unanimity of opinion among the various investigators and concluded that "it has not yet been demonstrated that the suprarenal influences the hypophysis, although this is probable" He pointed out that the short survival

24 Putnam, T J , Benedict, E B , and Teel, H M Studies in Acromegaly VIII Experimental Canine Acromegaly Produced by Injection of Anterior Lobe Pituitary Extract, *Arch Surg* **18** 1708 (April, pt 1) 1929

25 Thompson and Troppoli, cited by Cushing <sup>7</sup>

26 Collip, J B , Anderson, E M , and Thomson, D L The Adrenotropic Hormone of the Anterior Pituitary Lobe, *Lancet* **2** 347, 1933

27 Kraus, E J Zur Pathologie der basophilen Zellen der Hypophyse, *Virchows Arch f path Anat* **247** 421, 1923

28 Kiyono, H Die Histopathologie der Hypophyse, *Virchows Arch f path Anat* **259** 388, 1926

29 Berblinger, W Die Störungen der inneren Sekretion der Keimdrüsen und die Sexualhormone, *Klin Wchnschr* **7** 1673 (Sept 2), 1721 (Sept 9) 1928

30 Houssay, B A Relaciones entre la hipofisis y las suprarrenales, *Prensa med argent* **20** 1563, 1933

of the adrenalectomized animals and the severe malnutrition which may of itself cause changes in the pituitary are two serious obstacles that have been encountered in this work

Martin<sup>31</sup> has studied the effect of the adrenals on the pituitary. When complete adrenalectomy was performed on adult female and on normal and castrate male rats, it produced a marked decrease in the gonad-stimulating hormone of the anterior lobe. Changes in the cytologic picture of the hypophyses of these rats were also noted. A brief statement refers to a decrease in the size and staining reaction of the oxyphils (alpha cells) of the pars anterior. The effect on the basophils was not constant. A more detailed report is still to be made.

While we reviewed the literature on the subject, it occurred to us that the reports of cases of adrenal neoplasm similar to our own might include studies of the pituitary gland or give evidence of the disturbances which might be considered manifestations of pituitary disorders<sup>32</sup>. The following reports were found which tend to show that manifestations of pituitary disturbance may occur in the presence of an adrenal tumor. Oppenheimer and Fishberg<sup>33</sup> reported the case of a 24 year old man who had hypertension due to a tumor of the adrenal cortex and who had an acromegalic appearance. It cannot be gathered from this report whether or not the appearance antedated the other clinical signs.

Long and Gray<sup>34</sup> reported a case of metastasizing carcinoma of the adrenal cortex in a man aged 45 in whom an acromegalic appearance developed while he was under observation during the last six months of life. At autopsy casual sections of the pituitary were examined and were reported to show an "overgrowth" of eosinophilic and chromophobic cells with marked predominance of the former.

Mathias<sup>10</sup> described an 18 year old girl who had hypertrichosis with a well marked beard from the age of 3 years and at the age of 18 died of a metastasizing neoplasm of the adrenal cortex. Serial sections of the pituitary gland showed a marked "increase"<sup>35</sup> of the eosinophilic

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31 Martin, S. J. The Effect of Complete Suprarenalectomy on the Oestral Cycle of the White Rat with Reference to Suprarenal-Pituitary Relationship, *Am J Physiol* **100** 180, 1932.

32 Moehlig (Pituitary Gland and Suprarenal Cortex, *Arch Int Med* **44** 339 [Sept] 1929) has made the statement "that acromegaly is associated at times with tumor of the adrenal cortex" (p. 342), but he cites no references or cases.

33 Oppenheimer, B. S., and Fishberg, A. M. The Association of Hypertension with Suprarenal Tumors, *Arch Int Med* **34** 631 (Nov) 1924.

34 Long, H. W., and Gray, J. W. Acromegaly Associated with Adrenal Tumor, *M J & Rec* **119** 38, 1924.

35 Rasmussen (*Am J Path* **5** 263, 1929) has shown that estimates of increases are not reliable and that quantitative determination of the relative numbers of each type of cell is necessary in order to determine changes in number.

cells and an overgrowth of the chief cells, which in one place had the characteristic of the cells of an adenoma

In view of these reports the changes in the pituitary described in our case assume more significance. Elucidation awaits further evidence based on cases in man, like that of Crooke, as well as experimental proof to show that disturbances of the adrenal cortex may affect the pituitary gland functionally or structurally.

Finally, there is an interesting hormonal aspect to this case. As will be recalled, there was an enormous increase in the amount of estrogenic substance in the patient's urine, a normal amount in the blood and a negative Friedman test for pregnancy. Exactly the same observations were recorded in a case recently observed by Frank<sup>36</sup>. His patient was a 33 year old woman who presented essentially the same clinical syndrome as our patient and at necropsy was found to have a tumor of the adrenal cortex and no adenoma of the pituitary. These 2 cases led Frank to believe that in the future such hormonal findings may prove diagnostic of tumor of the adrenal cortex in contradistinction to adenoma of the pituitary, but he awaited further opportunities to confirm this suspicion.

Since our patient showed an unusual amount of atresia of the ovarian follicles and atrophy of the endometrial glands, we were at a loss to account for the source of the huge amount of estrogenic substance found in her urine. It therefore was of interest to us to learn that recently Migliavacca<sup>37</sup> showed experimentally in guinea-pigs, whose hypophyses had been irradiated to eliminate their hormonal influence, that a commercial preparation of adrenal cortex causes an intense luteinization of the ovarian follicles even in the presence of obliterating or cystic atresia of the follicles. Since Dr. Frank found somewhat larger amounts of estrogenic substance in the tumor material from our patients than in the material from an indifferent organ (spleen), it may be that the neoplasm was the source of the hormone.

#### SUMMARY

The case is reported of a 19 year old girl who presented hirsutism, hypertension, obesity and striae atrophicae in life and at necropsy was observed to have a metastasizing carcinoma of the adrenal cortex and an indeterminate miliary adenoma of the anterior lobe of the pituitary gland.

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36 Frank R. T. Suggested Test for Functional Cortical Adrenal Tumor, *Proc Soc Exper Biol & Med* **31** 1204, 1934.

37 Migliavacca, A. Irradiazione rontgen dell'ipofisi e riattivazione parziale dell'ovaio sotto l'azione dell'ormone corticosurrenale, *Ztschr f Zellforsch u mikr Anat* **17** 662, 1933.

Selective degenerative changes were noted in the nuclei of the beta cells of the pars anterior of the hypophysis

Although data are not conclusive, evidence is given which tends to show that the pituitary adenoma is not merely a coincidental finding

Attention is drawn to the co-existence of clinical manifestations or pathologic evidence of changes in the pituitary gland in similar cases of metastasizing adrenal neoplasm recorded in the literature, this and other evidence of the effect of adrenal disturbances on the pituitary gland are discussed

Marked overexcretion of estrogenic substance in the urine was noted during life, and this is discussed in relation to the atresia and atrophy of the ovaries and endometrium

# CONTROL OF HYPERTHYROIDISM FOLLOWING PARTIAL THYROIDECTOMY

BY REMOVAL OF UNUSUALLY SMALL AMOUNTS OF  
THYROID TISSUE

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The results of surgical treatment of exophthalmic goiter are today most gratifying and compare favorably with those of other operations of equal magnitude. As practiced at the Mayo Clinic, the operation of subtotal thyroidectomy, in which is preserved a posteromesial portion of each lobe equivalent to from a sixth to a third of a lobe of normal size, is comparatively free from technical complications, such as parathyroid tetany and injury to the inferior laryngeal nerve. Since the standardization of the preoperative treatment with iodine, the operation has been performed on approximately nine thousand patients with exophthalmic goiter, with a mortality of 0.8 per cent. The late results are equally gratifying. Within from two to four weeks after operation the basal metabolic rate is usually within normal limits, and after the lapse of one, three and five years more than 90 per cent of the patients consider themselves improved or as well as they were before the onset of the disease and present evidence to indicate that they are free from hyperthyroidism. It is estimated that the death rate for patients who have successfully undergone thyroidectomy is no greater than that for an average group of persons.

It is also estimated that after the lapse of five years from 2 to 5 per cent of the patients have sufficient evidence of recurrence of symptoms to warrant a secondary operation. In nearly all cases of recurrent exophthalmic goiter regeneration of the remaining portion of the thyroid gland takes place, so that the examiner usually is able to palpate some thyroid tissue, although it is common at operation to find far greater enlargement of the gland than was indicated on physical examination. The reason for the failure of the examiner to estimate the size of the gland more accurately is that the greater portion of the enlargement may be concealed as retrotracheal or substernal projections which are beyond the reach of his fingers. This tendency in cases of recurrent

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goiter for the remaining portion of the thyroid gland to project behind the trachea and into the upper part of the mediastinum is readily explained by the presence of scar tissue, which commonly forms in front of the resected portion of the lobe. Since scar tissue is more unyielding than other soft structures of the neck, any subsequent growth of the thyroid gland will naturally project in the direction of least resistance, that is, retiotracheally or substernally. These facts are mentioned only to emphasize the point that in cases of suspected recurrent hyperthyroidism failure to palpate any appreciable amount of thyroid tissue does not necessarily exclude the presence of such tissue.

Several factors may be responsible for recurrence. Some of the probable factors are the amount of thyroid tissue left at operation, the recurrence or persistence and the intensity of the unknown force causing the disease and persistence in the postoperative use of iodine. Undoubtedly other factors also exist. Some patients with recurrent exophthalmic goiter may have the evidences of the disease brought permanently and completely under control by the use of compound solution of iodine alone, while in many cases further resection of the thyroid gland is necessary to bring the disease under complete control. All the factors which determine the controllability with iodine are not known, but in a study of a group of these cases it immediately becomes apparent that the amount of thyroid tissue present is an important factor. A large proportion of patients with recurrent exophthalmic goiter who have such a small remnant of thyroid gland that it cannot be palpated will easily lose all symptoms and signs of exophthalmic goiter after compound solution of iodine has been administered for two weeks or more. In a recent study of a series of cases of recurrent exophthalmic goiter it was found that in 25 per cent the symptoms were so controlled.<sup>1</sup> In most of these cases the disease will be kept under control for years at least by the continued administration of iodine. The majority of patients with a more easily palpable thyroid gland at the time of recurrence will not have the disease sufficiently controlled by iodine to warrant further avoidance of surgical treatment, and in these cases further resection of the thyroid gland has been resorted to in this clinic in order to complete the control of the disease. The latter procedure has been carried out also whenever control of hyperthyroidism has not been obtained within a few weeks by the administration of iodine.

The three cases reported here are of interest because of the maintenance of the amount of thyroid tissue present at the time of the recurrence of exophthalmic goiter and because of the reactions of the patients both before and after a second operation.

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<sup>1</sup> Haines, S. F. The Use of Iodine in Recurrent Exophthalmic Goiter, *West J. Surg.* **42**: 449 (Aug.) 1934.



## REPORT OF CASES

CASE 1—A married woman 31 years of age was first seen at the clinic in June 1925, when she was examined because of obesity. The basal metabolic rate at that time was +5 per cent, and the blood pressure in millimeters of mercury was 118 systolic and 88 diastolic. A restricted diet was outlined for the patient but was not followed, and the weight increased to 280 pounds (127 Kg). In 1930 the dietary restriction was rigidly adhered to, and 112 pounds (50.6 Kg) was lost in nine months. During that time the patient complained of dyspnea on exertion and of insomnia, there had been short attacks of palpitation for three months and some looseness of the stools for one month. On March 23, 1931, the patient was again examined. She was nervous and emotionally upset, the skin was warm and there was a slight fine tremor of the fingers. The thyroid gland was palpable

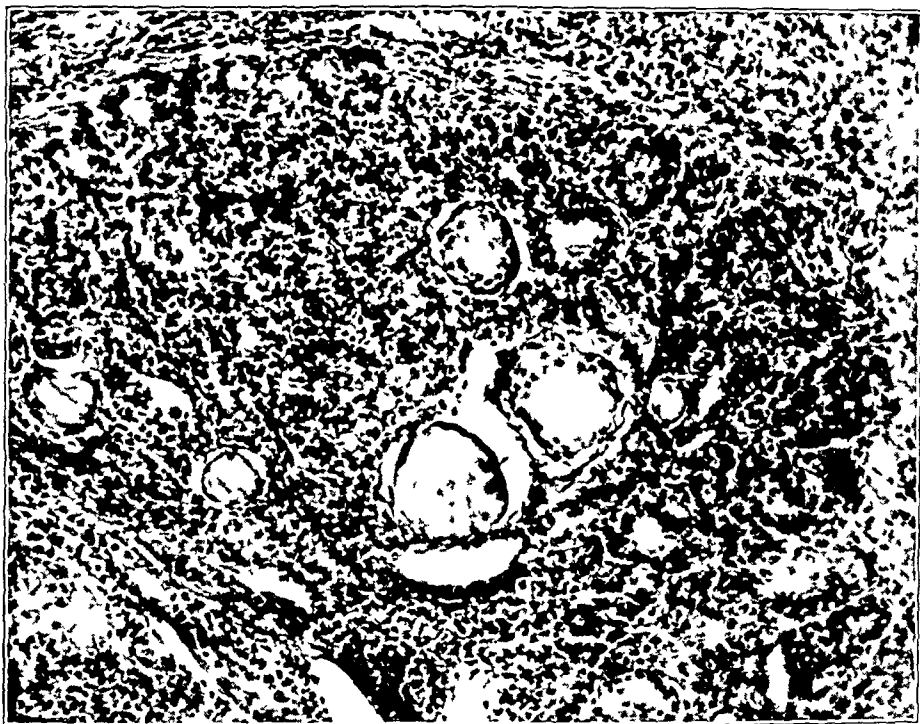


Fig. 1—Hypertrophic parenchymatous thyroid tissue, showing moderate thyroiditis and slight fibrosis

and firm. The basal metabolic rate on three consecutive days was +52, +43 and +44 per cent. The readings of the systolic and the diastolic blood pressure were 140 and 84, 134 and 70, and 130 and 78, respectively.

The patient was given 10 minims of compound solution of iodine three times daily, and the basal metabolic rate after six days was +30 per cent and after eleven days +27 per cent. There was marked improvement in the patient's nervous state and strength. On April 9 partial thyroidectomy was performed. The thyroid gland was small and hard, the lobes being very slightly larger than normal. The amount of tissue preserved was estimated to be about a fifth of a normal-sized lobe on the right and about a fourth of a normal-sized lobe on the left. Pathologic examination of the excised portions of thyroid gland revealed hypertrophic parenchymatous tissue, with evidence of moderate thyroiditis and fibrosis (fig. 1). The total weight of the tissue removed was 6 Gm. For six weeks after

the operation the patient's condition was improved. She had attacks of palpitation, but these were rare. She then noticed a loss of strength, increased nervousness and mental unrest. The attacks of palpitation increased in frequency and were associated with tachycardia, giddiness and weakness. There had been constant anorexia since thyroidectomy was performed and a loss of 5 pounds (2.3 Kg.)

The patient returned for examination on September 15. The blood pressure on two occasions was 130 systolic and 60 diastolic and 142 systolic and 72 diastolic, the pulse rate ranged from 102 to 104 beats per minute. The skin was warm, and there was marked weakness of the quadriceps muscles. The thyroid gland was not palpable. The basal metabolic rate on two occasions was +44 and +46 per cent. The patient was still taking compound solution of iodine. On September

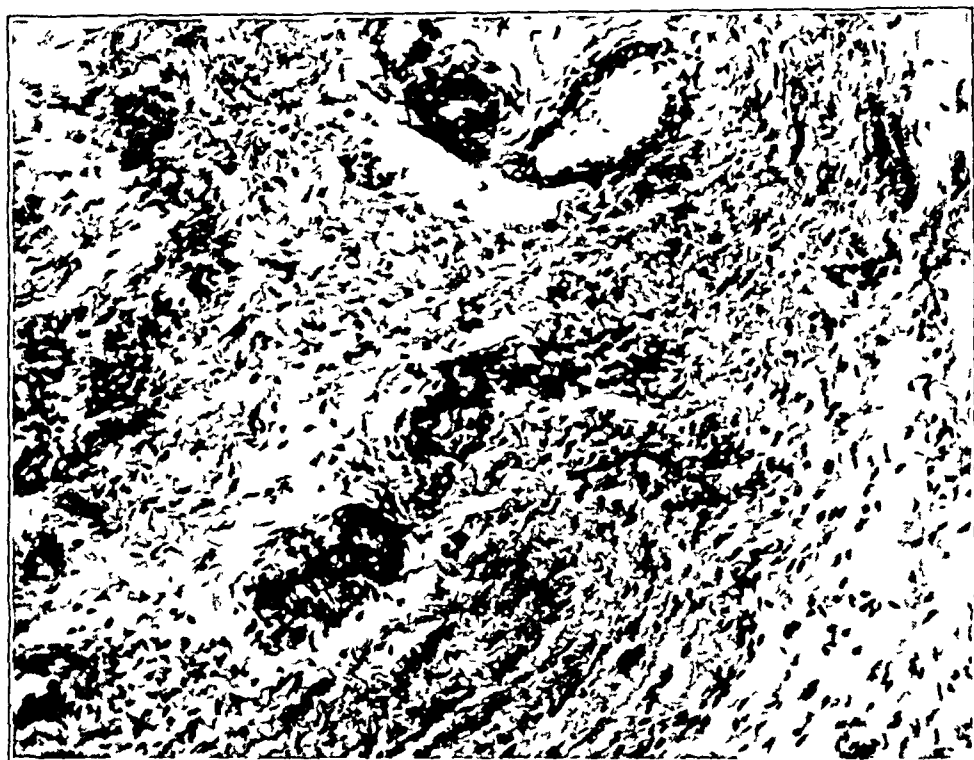


Fig 2—Scar tissue containing a very few thyroid acini

18 and 19 treatment with roentgen rays was given over the thyroid gland, and the patient was allowed to return home, with instructions to continue the use of iodine.

On October 14 the patient returned to the clinic. There was such marked weakness of the thighs and legs that she had fallen frequently and was considerably bruised. Also, she had fainted a number of times. The basal metabolic rate was +40 and +44 per cent on two occasions, and readings of the systolic and the diastolic blood pressure were 136 and 76, and 140 and 78, respectively. Further resection of the thyroid gland was undertaken on October 23. The amount of thyroid tissue on each side was estimated at less than a tenth the size of a normal-sized lobe. No thyroid tissue could be revealed retrotracheally or substernally. A very small amount of tissue was removed from each side, one portion containing more parathyroid than thyroid tissue. The right inferior thyroid artery was ligated. Less than 1 Gm of tissue was removed. Microscopically, the excised tissue consisted partly of parathyroid tissue and partly of scar tissue containing

very few thyroid acini (fig 2) On October 28 the basal metabolic rate was +18, on October 30, +11, and on November 4 +1 per cent The basal metabolic rate was determined daily and showed a constant gradual fall till November 11, when it reached -6 per cent

At that time the patient was enthusiastic about the state of her health However, on December 15 she returned, complaining of fatigue, of lack of energy and endurance and of excessive sleepiness, so that a nap of two or three hours was necessary in addition to thirteen hours of sleep at night She was very intolerant to cold She had noticed swelling of the face, neck and abdomen since the latter part of November The weight had increased 19 pounds (8.6 Kg) since the second operation Her appearance was typical of myxedema, the skin was dry, scaling and cold, there was edema of the subcutaneous tissues, the recovery of the

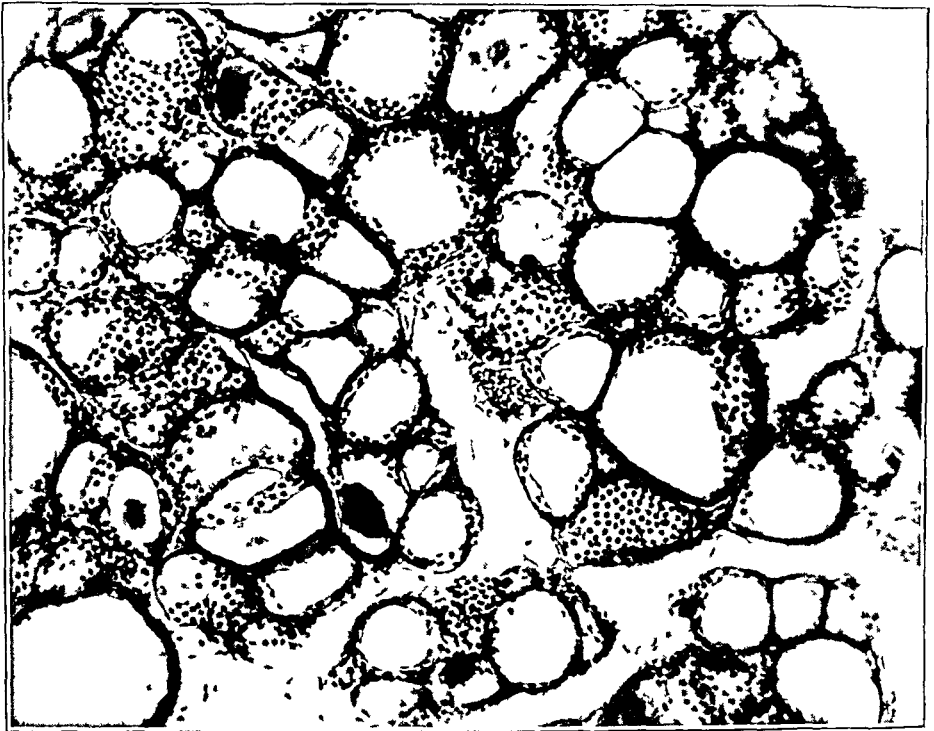


Fig 3—Colloid thyroid tissue

tendon reflex was slowed and the voice was low, hoarse and slow The basal metabolic rate was -16, -16 and -17 per cent on three occasions The value for cholesterol was 407 mg per hundred cubic centimeters of blood One gram (0.065 Gm) of thyroid was given daily, and the basal metabolic rate rose to -5 and -6 per cent The cholesterol content was 222 mg per hundred cubic centimeters of blood

On Jan 12, 1932, the patient was seen for the last time The basal metabolic rate at that time was -9 per cent, and there were no evidences of organic disease She was pregnant for the first time in twelve years of married life She had a normal delivery of a normal child In October 1932 she reported that she was still taking thyroid and was well

CASE 2—A man aged 37 was examined on Aug 12, 1930 Eight years before, in the course of a general examination, the basal metabolic rate was +8 per cent Readings of the systolic and diastolic blood pressure at that time were 138 and

100, 124 and 82, and 118 and 80, respectively, the pulse rate varied from 72 to 116. At the time of examination at the clinic he had a history of nervousness, rapid heart beat, headache, insomnia and palpitation and tachycardia for five months. There was marked tremor of the hands. The patient was restless and stimulated. The thyroid gland was easily palpable, each lateral lobe measuring 2.5 by 5.5 cm. The blood pressure was 150 systolic and 90 diastolic and the pulse rate 120. The basal metabolic rate was +13 per cent. The patient was unable to remain under observation at the time, but on September 12 he returned. The basal metabolic rate was +30 and +26 per cent on two occasions. There were frank clinical evidences of exophthalmic goiter. Ten drops of compound solution of iodine was given three times a day. On September 24 the basal metabolic rate was

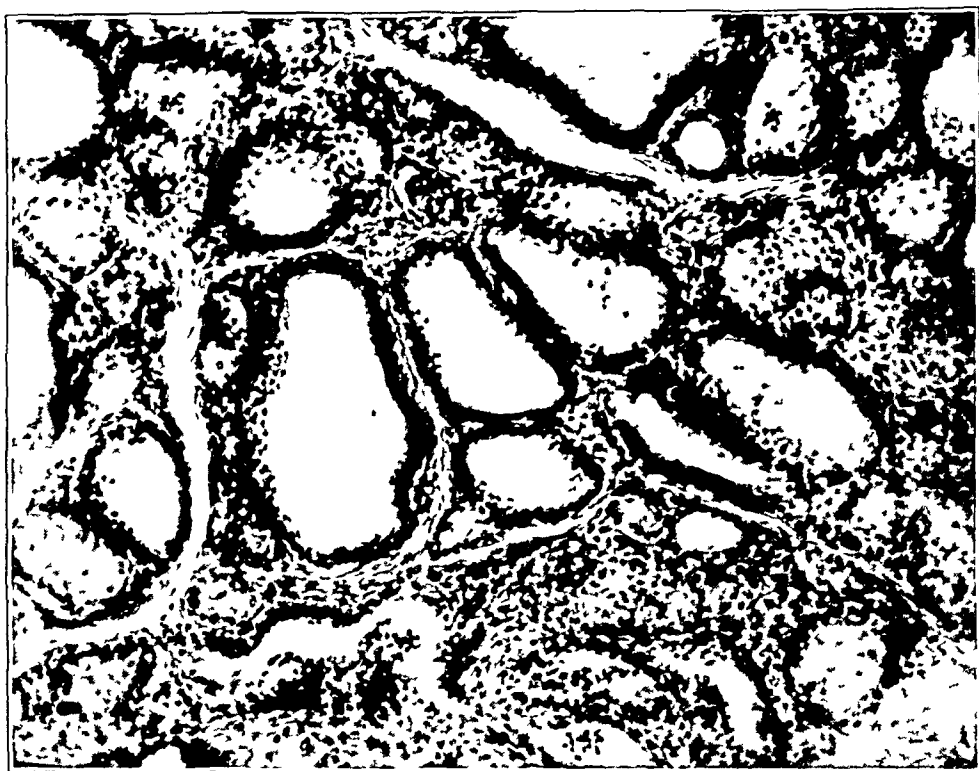


Fig 4—Hypertrophic parenchymatous thyroid tissue

+14 per cent, and there had been a definite improvement in the patient's condition. On September 26 partial thyroidectomy was performed, and 18 Gm of tissue was removed, leaving an amount of the posterior part of each lobe equal to about a fourth of a normal-sized lobe. Pathologic examination of the excised portions of gland revealed colloid thyroid tissue (fig 3).

The patient was seen again on November 18. He had felt perfectly well until two weeks previously, when he had again noted nervousness, insomnia, headache in the frontal region and abnormal stimulation. The remnant of thyroid gland was not palpable. There was slight tremor of the fingers, and the skin was warm and moist. The blood pressure was 142 systolic and 90 diastolic and the pulse rate 94. The basal metabolic rate was +12 and +11 per cent on two occasions. Iodine was again given, and by December 6 the basal metabolic rate had gradually fallen to -2 per cent, with subsidence of symptoms. After this the patient took iodine irregularly, and on Jan 5, 1931, the basal metabolic rate had risen to +8 per cent,

and there was clinical evidence of hyperthyroidism. The condition was again controlled by the regular use of iodine, and the basal metabolic rate was reduced to  $-5$  per cent. From then until September 17 the patient's condition varied from time to time. On several occasions there were evident exacerbations of hyperthyroidism, with the basal metabolic rate as high as  $+22$  per cent. There seemed to be gradually increasing evidence of hyperthyroidism over the entire period. Compound solution of iodine was taken during most of this time. In September and October 1931 three courses of roentgen treatment over the thyroid gland were given. There seemed to be no apparent benefit from this, but the amount of treatment was not great. On November 17 the patient was bothered so much by symptoms of hyperthyroidism that he decided to follow the advice previously given to have another portion of the thyroid gland removed. The last pre-



Fig 5—Colloid thyroid tissue

vious determination of the basal metabolic rate had been made on October 29 and was  $+13$  per cent. At operation the right lobe was observed to be about a fourth and the left lobe about a fifth as large as a normal lobe. Very small bits of thyroid tissue were removed from each lobe and from the left lateral wall of the trachea. Glandular tissue amounting to about an eighth or a tenth of a normal-sized lobe was preserved on the left side, and tissue amounting to about a fifth of a normal-sized lobe was preserved on the right. The tissue removed weighed 1 Gm and was reported pathologically as hypertrophic parenchymatous thyroid tissue (fig 4). The basal metabolic rate was determined frequently, the dates and results being as follows: November 23,  $+19$  per cent, November 25,  $+12$  per cent, November 30,  $+9$  per cent, December 5,  $+2$  per cent, and Jan 25, 1932,  $-8$  per cent. At the time of the last test the patient felt perfectly well and had no clinical evidence of hyperthyroidism.

In May 1932 the patient was again examined. At that time he said he had been nervous, had had palpitation and had lost 5 pounds (2.3 Kg.) during the previous two months. The basal metabolic rate was +2 per cent. He was still taking compound solution of iodine and was advised to continue doing so. In September 1932 he wrote that his health was excellent. His health continued to be good until April 1934, when he suddenly dropped dead. Permission for necropsy was not obtained.

CASE 3—A woman aged 51 was seen first on March 1, 1932. She gave a history of hyperthyroidism of fluctuating intensity for twenty months. During that time she had had a basal metabolic rate varying from +40 to +60 per cent, and she had taken iodine intermittently throughout the period of illness. The thyroid gland could not be outlined definitely. There were marked tremor and weakness



Fig. 6—Colloid thyroid tissue with evidence of thyroiditis

of the quadriceps muscles. The blood pressure was 138 systolic and 76 diastolic and the pulse rate 118. The basal metabolic rate was +50 and +43 per cent on two occasions. During treatment with iodine the basal metabolic rate dropped to +18 per cent, and a gain in strength and a reduction of nervousness were noted. On March 15 partial thyroidectomy was performed. The gland did not look like the usual exophthalmic goiter. Three grams of tissue was removed, and the pathologic examination revealed that it was from a colloid thyroid gland (fig. 5). On March 19 the basal metabolic rate was +7 per cent, and the patient's condition was improving.

On April 17, 1933, the patient returned to the clinic. For one month after her postoperative dismissal her condition had improved steadily. Then she had noted a recurrence of the tremor and had lost weight and strength. Iodine had been taken intermittently. The skin was hyperemic and moist. Marked tremor of the

fingers and weakness of the quadriceps muscles were noted. The blood pressure was 138 systolic and 82 diastolic and the pulse rate 140. No thyroid tissue could be felt. While the patient was at rest in the hospital the pulse rate varied from 93 to 116 beats per minute. At three consecutive tests the basal metabolic rate was +21, +12 and +7 per cent. The picture was frankly that of recurrent exophthalmic goiter. Compound solution of iodine, 10 drops three times daily, was prescribed, and the patient returned home temporarily. On June 5 she reentered the hospital. She had noted a moderate improvement in her condition. The blood pressure was 142 systolic and 92 diastolic and the pulse rate 120. Weakness of the quadriceps muscles, which had previously been graded 4, was now graded 2 plus. The clinical evidences of hyperthyroidism seemed definite. Only one test of the basal metabolic rate was made, as the patient had decided to undergo further resection of the thyroid gland and did not wish to delay it, this rate was +34 per cent and was probably not basal, as the patient was very nervous. The operation was performed on June 6. Very small remnants of thyroid tissue were observed on both sides of the trachea. About half the thyroid tissue was removed, and the right inferior thyroid artery was ligated. The fragments of tissue removed revealed the presence of a colloid thyroid gland with evidences of thyroiditis.

*Determinations of the Basal Metabolic Rate, Blood Pressure and Pulse Rate in Case 3*

1933	Basal Metabolic Rate, Percentage	Blood Pressure		Pulse Rate
		Systolic	Diastolic	
June 13	+12	124	65	96
June 16	+ 4	112	70	89
June 19	— 4	120	78	91
June 23	— 8	110	80	75

(fig 6), they weighed less than 1 Gm. Subsequent observations of the basal metabolic rate, blood pressure and pulse rate are given in the accompanying table.

During this time there was a gain in weight of 7 pounds (3.2 Kg). The patient was much more quiet, the skin became cooler and less moist and the tremor diminished. The strength increased rapidly, and the weakness of the quadriceps muscles at the time of the patient's dismissal was graded 1 plus.

In a letter dated Sept 19, 1933, the patient reported a continuous and marked improvement in general health and stated that she could do much more without fatigue. The basal metabolic rate taken at home was reported as —24 per cent. In January 1934 she lost weight, and the pulse rate increased. She was reported to have a basal metabolic rate of +51 per cent. However, by the first part of February she was again improving, and the basal metabolic rate was reported to be normal. In June 1934 the patient was again examined. The basal metabolic rate was —11 per cent, and there was no clinical evidence of thyroid disturbance.

#### COMMENT

The first patient presented at the time of the recurrence a much more severe degree of intoxication than would have been anticipated from the amount of thyroid tissue remaining. At first certain hysterical features made us doubt the accuracy of the basal metabolic tests, but the clinical

manifestations of exophthalmic goiter were sufficiently characteristic to overcome that doubt. The second operation was postponed for a long time in the hope that there would be a subsidence in the intensity of the disease. The relief from symptoms which occurred within a week of operation was striking and the beneficial effects of the second resection were unquestionable. At the time of dismissal the patient emphatically stated that she was in better health than she had been for years. Her opinion was corroborated when the basal metabolic rate had been brought to normal after the treatment of myxedema.

The second patient probably had had mild hyperthyroidism at times since the second operation, but this condition apparently had subsided, and the patient's health was good until the time of his death, two and a half years after the last operation, from causes apparently not associated with thyroid disease. This patient was being seen at the time the result of the second thyroidectomy in case 1 became evident, and this encouraged us in advising a second resection in case 2 also. Case 3 corresponded to the other cases except that evidence of parenchymatous hypertrophy was not observed in the thyroid tissue removed at either of the two operations.

Phemister and Delaney<sup>2</sup> have reported a case which was similar in some respects to our case but in which no thyroid tissue was identified at necropsy.

The three cases reported are of special interest because of the very small amount of thyroid tissue observed at the time of the second operation and because of the excellent results obtained by further resection. As only 1 Gm. or less of thyroid tissue was removed in each case, the question naturally arises whether a secondary operation would have been necessary in these cases if a gram more of tissue had been removed originally. The answer is not known, but it is our opinion that this procedure would not necessarily have prevented recurrence of hyperthyroidism, furthermore, we are convinced that it is still possible for the two surviving patients, who now have only a minute amount of thyroid tissue, to have further recurrence of the disease.<sup>3</sup> In other words, after subtotal thyroidectomy for exophthalmic goiter, in which 65 to 85 per cent of the tissue is removed, the degree of activity of the remaining portion of the gland is dependent not wholly on the size of the gland but rather, and to an important extent, on the persistence or recurrence of the stimulus that originally produced the disease. There

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2 Phemister, D. B., and Delaney, P. A. Thyrotoxicosis Continuing After Extreme Operative Iodine and Roentgen Therapy, *J. A. M. A.* **100** 586 (Feb 25) 1933.

3 Pemberton, J. deJ. Recurring Exophthalmic Goiter. Its Relation to the Amount of Tissue Preserved in Operation on the Thyroid Gland, *J. A. M. A.* **94** 1483 (May 10) 1930.



is clinical and pathologic evidence to indicate that after subtotal thyroidectomy there follows in a large proportion of cases actual subsidence of the disease rather than abatement of the symptoms alone

#### SUMMARY

Three cases are presented in which recurrence of exophthalmic goiter occurred when the remaining amount of thyroid tissue was so small as not to be palpable. In none of these cases was control of hyperthyroidism achieved by the administration of compound solution of iodine. A second operation in each case revealed such a small amount of thyroid tissue that not more than 1 Gm. could be removed. Control of hyperthyroidism was accomplished in each case after the removal of this small amount of tissue.

# GENERALIZED DISCOLORATION OF SKIN RESEMBLING ARGYRIA FOLLOWING PROLONGED ORAL USE OF BISMUTH

A CASE OF "BISMUTHIA"

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Argyria is so striking a condition that its recognition is easy. Usually the diagnosis is made by inspection alone. Recently a patient with a deep blue discoloration of the skin and mucous membranes entered ward 15 of the Cook County Hospital complaining of severe diarrhea. At first the condition was considered to be argyria, but when the patient was questioned the possibility of bismuth poisoning appeared. A number of years before the patient had been told that he had a peptic ulcer. He thought the medicine given at that time was silver nitrate. Later diarrhea appeared. It had persisted for eighteen years, during which time he had ingested large amounts of bismuth salts.

Since large amounts of the less soluble bismuth compounds have been given orally to patients in the past without fear, this case seemed unusual. Histologic and chemical studies of the skin definitely excluded silver and established bismuth as the cause of the pigmentation. No mention has been found in the available literature of permanent generalized discoloration of the skin and the mucous membranes. The term "bismuthia" is suggested for the condition.

## REPORT OF CASE

*History*—J H, a white man born in Tennessee, entered the Cook County Hospital complaining of abdominal distress, occasional vomiting and diarrhea, for the past eighteen years. In 1916 he fell 52 feet (15.8 meters) from a scaffolding on which he had been doing carpenter work. He was picked up semistuporous

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and taken home and was confined to his bed for eighteen months. A short but undetermined time prior to the accident, diarrhea appeared, which had been constantly present. He had from two to ten movements daily, the stools frequently containing mucus and pus and rarely small amounts of blood. When they were first noted, these frequent watery discharges were controlled by a mixture of 20 grains (1.2 Gm) of bismuth subnitrate and sufficient camphorated tincture of opium to make 1 drachm (4 cc). He complained of intermittent gnawing pains, griping attacks of colic and vomiting. Relief from these symptoms was

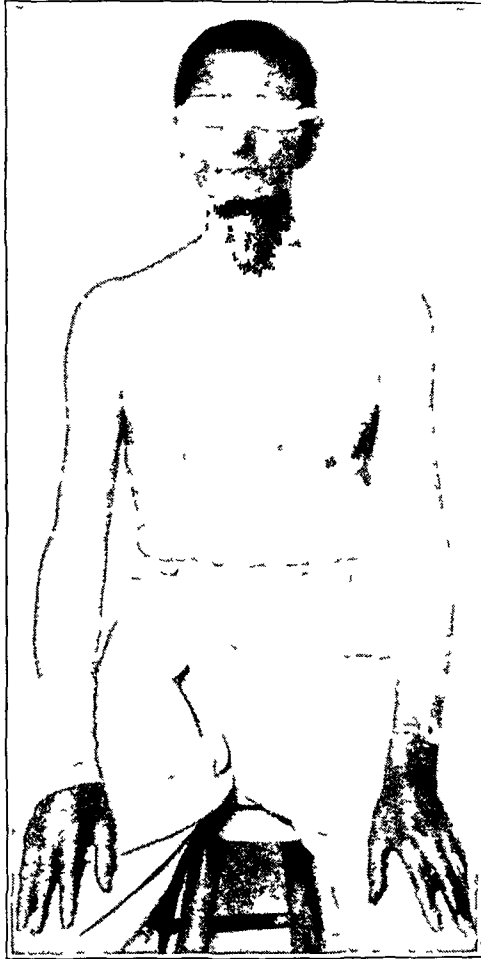


Fig 1—Photograph of the patient, showing the unevenness of the pigmentation

attained by the continual use of the aforementioned mixture, often as much as 4 ounces (120 cc) daily was needed. During February 1918, while he still had fair skin and very light reddish hair, he began to notice a steel-gray discoloration. Only three days later, to use the patient's words, "I turned the color I have been ever since." Subsequent to this, various other compounds of bismuth, such as the subcarbonate, the subgallate and the oxide, were used in amounts of from 10 to 30 grains (0.6 to 2 Gm) per dose. Despite his discomfort he managed to maintain his body weight until four months before his second admission.

There was a hemorrhoidectomy in 1916. The patient had had chronic alcoholism for fifteen years prior to admission.



Fig 2—Portrait of the patient painted from life



*General Examination*—The patient was slender and slightly emaciated, and his skin was colored deep blue-gray, with a distinct metallic sheen. The hair was thin and of fine texture, with a deep mahogany shade. Both pupils were round and regular and reacted to light and in accommodation, but the somber gray conjunctiva gave the eyes a glassy, cadaveric appearance. All the teeth had been removed, and the buccal and pharyngeal mucous membranes were a deep indigo-purple-black. Neither the cervical glands nor the thyroid gland were palpable. The patient was of the asthenic habitus, with a long, thin, symmetrical chest, the lungs and the heart were essentially normal except for the accentuated aortic second tone. The blood pressure was 152 systolic and 90 diastolic. Slight tenderness was elicited in the abdomen, especially in the epigastric region and the left lower quadrant. Rectal examination revealed internal and external hemorrhoids.

The discoloration of the skin was the most striking feature. It was a universal pigmentation, being most prominent and of the richest color over the forehead, face and neck and the dorsa of the hands (fig 1). No description of the color of the face is adequate (fig 2). As the result of burns, cuts and bruises, the dorsa of the hands were mottled with many light pearly-gray scars. The skin of the remainder of the body was of a drab, ashen hue, being lightest at the inner aspects of the thighs and over the scrotum.

Nothing abnormal was found in the urine or in the blood chemistry, and a negative Kahn reaction was recorded. Secondary anemia was present, with 2,680,000 red blood cells and a hemoglobin content of 70 per cent, while there were 7,900 leukocytes per cubic millimeter. Roentgenographic and fluoroscopic examination of the duodenum showed an ulcer, but the rest of the gastro-intestinal tract was normal. A mixture of 6 per cent sodium thiosulfate and 0.66 per cent potassium ferricyanide in distilled water was injected as superficially as possible in the skin over the right trochanter. Immediate blanching of the skin about the site of injection followed this modification of the Stillians and Lawless test<sup>1</sup>. Under these conditions, patients with argyria show a similar blanching of the skin.

Nearly one year later he entered the hospital with impending delirium tremens. After three days he was much improved, however, he continued to have a low grade fever. A roentgenogram of the chest showed marked infiltration of the upper third of the left lung field, which in addition to the clinical findings assured the diagnosis of ulcerocaseous tuberculosis.

*Histologic Examination*—A specimen of the skin was taken for biopsy from the dorsum of the right hand, where the pigmentation was very deep. Microscopic examination showed innumerable small granules of a metallic nature in the capillary and reticular layers of the dermis (fig 3).

*Chemical Examination of the Skin for Bismuth*—A piece of skin 4.5 by 2.5 cm was removed from the area overlying the left greater trochanter. It was placed in a new clean sillimanite dish and ashed in an electric muffle furnace at 500 C ( $\pm 10$  C) for eighteen hours. The ash was a pale cream-white powder. Any mercury that might have been present would have been volatilized by this treatment. The ash was moistened with dilute nitric acid and evaporated on a steam bath until almost dry, then a small amount of dilute hydrochloric acid (5 per cent) was added. This was allowed to remain on the steam bath for several hours, after which it was filtered through a fine-grained filter paper. Any silver present in the tissue would have been converted by this procedure to silver chloride,

<sup>1</sup> Stillians, A. W., and Lawless, T. K. The Intradermal Treatment of Argyria, J. A. M. A. 92:20 (Jan 5) 1929.

which would then remain as a residue on the filter paper. The filtrate was clear and free from opalescence. After the filter paper was washed with hot water, it was extracted with a warm dilute solution of ammonium hydroxide. The extract after filtration was rendered acid to litmus by the addition of dilute hydrochloric acid. No opalescence or precipitate formed. This showed absence of silver.

The filtrate obtained from the treatment with hydrochloric acid would be expected to contain other metallic salts. It was placed in a small evaporating dish, and 2 cc of concentrated sulfuric acid was added. It was then evaporated slowly on an electric hot plate until fumes of sulfur tri-oxide were evolved. After cooling, the contents of the dish were diluted by the addition of 100 cc of water and 100 cc of 95 per cent ethyl alcohol and allowed to stand overnight. The absence of a precipitate at that point indicated that lead was not present. The filtrate was evaporated to a volume of 100 cc, placed in an Erlenmeyer flask and



Fig 3—Photomicrograph of a section of the skin. There are many small metallic granules in the capillary and reticular layers.

saturated with hydrogen sulfide gas. A small amount of dark brown, somewhat flocculent precipitate formed. After standing overnight the solution was again saturated with hydrogen sulfide and filtered. The filter paper containing the brown precipitate was washed first with distilled water which had been saturated with hydrogen sulfide and then with warm, freshly filtered ammonium polysulfide solution (to remove any traces of arsenic, antimony or tin) and finally with a saturated solution of hydrogen sulfide in water. The dark brown sulfide precipitate which remained was readily soluble in warm dilute hydrochloric acid. This acid solution was carefully evaporated in a small siliimanite dish on a steam bath until just dry. The faint crust of residue was white and when moistened with a drop of ammonium hydroxide it gave no trace of blue coloration (absence of copper). This indicated that the sulfide was that of bismuth. The residue was barely acidified with hydrochloric acid and again precipitated by the addition of cold water which had been

saturated with hydrogen sulfide. By comparison of the intensity of the dark color produced by this precipitate with that obtained from known amounts of bismuth, the quantity present was estimated to be 0.05 mg ( $\pm 0.01$  mg).

*Chemical Examination of the Urine for Bismuth*—The presence of bismuth in the skin raised the question of bismuth in circulation. Two twenty-four hour specimens of urine were collected from the patient, evaporated to dryness, ashed and tested for bismuth by means of the quinine potassium iodide reaction of Aubry.<sup>2</sup> These tests gave negative results for bismuth.

#### COMMENT

It is generally assumed that the less soluble salts of bismuth taken by mouth are harmless, yet a number of deaths from bismuth poisoning have been reported. The exact mode of death was not always the same. Impurities, such as arsenic,<sup>3</sup> zinc and lead,<sup>4</sup> the results of improper manufacture and purification of the bismuth salts, caused many fatalities. Some blamed the cations,<sup>5</sup> while a few held the metal responsible.<sup>6</sup> The experiments of Bohme were conclusive and classic.<sup>7</sup> He found that bismuth subnitrate when mixed in a test tube with feces from human beings (particularly of children) liberated nitrites. Early death after the ingestion of large amounts of bismuth subnitrate simulated that caused by poisoning with sodium nitrite. In both cases there were an acute onset, increasing dyspnea, methemoglobinemia and death. Thus, he concluded, poisoning from bismuth subnitrate was really a nitrite phenomenon. Since then methemoglobinemia has been frequently demonstrated, and recently Roe<sup>8</sup> reported the death of a 1 month old infant who had been given 190 grains (13 Gm.) of bismuth subnitrate.

In a few cases intoxication followed the use of dusting powder containing bismuth salts. As early as 1882 Kocher<sup>9</sup> reported cases of

2 Aubry, P. Recherche du bismuth dans l'urine, J de pharm et chim **25** 15, 1922.

3 (a) Goadby, Kenneth. Diseases of the Gums and Oral Mucous Membranes, ed 4, New York, Oxford University Press, 1931, p 356. (b) Fullerton, H S. Case of Poisoning by Impure Nitrate of Bismuth, Am J M Sc **67** 280, 1874. (c) Salisbury, J H. Arsenic in Subnitrate of Bismuth, Chicago M J & Exam **36** 601, 1878.

4 Webster, R W. Legal Medicine and Toxicology, Philadelphia, W B Saunders Company, 1930, p 475.

5 Schumm. Spektroskopischer Nachweis der Bismuthum subnitricum Vergiftung, Deutsche med Wchnschr **36** 1250, 1910.

6 Lewin, L. Ueber Wismutvergiftung und einen ungiftigen Ersatz des Wismuths für Röntgenaufnahmen, München med Wchnschr **56** 643, 1909.

7 Bohme, A. Ueber Nitrivergiftung nach interner Darreichung von Bismuthum subnitricum, Arch f exper Path u Pharmacol **57** 441, 1907.

8 Roe, H E. Methemoglobinemia Following the Administration of Bismuth Subnitrate. Report of a Fatal Case, J A M A **101** 352 (July 29) 1933.

9 Kocher, T. Ueber die einfachsten Mittel zur Erzielung einer Wundheilung durch Verklebung ohne Darmrohren, Samml klin Vortr no 224, 1882 (Chir no 72), p 1917.



stomatitis, progressing to ulceration, diphtheritic gingivitis, dysphagia, nephritis, nausea and diarrhea, following the use of bismuth subnitrate as a dusting powder on freshly granulating wounds. One patient who came to autopsy had large purple areas of ulceration throughout the mucous membranes of the colon and the terminal portion of the ileum.

Mixtures of salts of heavy metals and petrolatum were used by surgeons about thirty years ago to obliterate sinuses and troublesome cavities, again drawing attention to bismuth. In 1909 Beck<sup>10</sup> stressed the dangers of his paste (a bismuth-petrolatum mixture containing 33 per cent of bismuth subnitrate). Severe toxic reactions occurred in three of his patients. "In many cases I have noted a slight lividity of the mucous membranes of the skin and a bluish border at the margin of the teeth, otherwise conditions were perfectly normal." The nausea, vomiting and albuminuria which followed the use of his paste gradually disappeared after its removal. He warned that not more than 100 Gm of the paste should be used in any case, suggesting that a reduction of the 33 per cent bismuth subnitrate content be made when larger quantities of the paste were necessary. A few years later he was able to report eleven cases in which the patient was treated with the paste, but in 30 per cent of them there was pigmentation of the gums<sup>11</sup>. In a later series of 1,800 cases without a fatality,<sup>12</sup> he curiously enough gave specific direction for the prompt removal of the paste by oil when toxic symptoms arise. A Negro into whose thorax 1,250 cc of the paste had been injected to obliterate an empyema cavity was reported by Higgins<sup>13</sup> to have shown signs of bismuth poisoning within two weeks after the operation. The evacuation of the bismuth paste resulted in the prompt healing of the oral lesions, but the steel-blue line along the borders of the gums persisted.

Many cases of toxic reactions from the paste were observed. Six of twenty-five orthopedic patients requiring treatment in the Cook County Hospital who were treated with Beck's paste showed blue lines on their gums. Less than 10 ounces (311 Gm) of the mixture had been given to four of these patients<sup>14</sup>. David and Kauffman, working

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10 Beck, E. G. Toxic Effects from Bismuth Subnitrate, with Reports of Cases to Date, *J A M A* **52** 14 (Jan 2) 1909.

11 Beck, E. G. The Surgical Treatment of Tuberculous Sinuses, *Tr Internat Cong Tuberc* **2** 219, 1908.

12 Beck, E. G. Bismuth Paste in Chronic Suppurative Sinuses and Emphysema, *J A M A* **67** 21 (July 1) 1916.

13 Higgins, W. H. Systemic Poisoning with Bismuth, *J A M A* **66** 648 (Feb 26) 1916.

14 David, V. C., and Kauffman, J. R. Bismuth Poisoning. Two Cases, with One Fatality, Following Injection of Bismuth-Vaseline Paste, *J A M A* **52** 1035 (March 27), 1953 (June 12) 1909.

under the direction of Prof Walter S Haines, were able to detect bismuth in excised bits of the affected mucous membranes Cabot<sup>15</sup> and Warfield<sup>16</sup> each reported fatalities from the use of Beck's paste Mayer and Baehr in their clinicopathologic studies of bismuth poisoning in 1912 found reports of seventy cases and twenty-six deaths in the literature<sup>17</sup> Since then, pigmentation of the mucous membranes and the blue line of the gums have been frequently mentioned They followed the use of bismuth pastes, particularly a bismuth-iodoform-paraffin paste<sup>18</sup>

The use of bismuth compounds as spirocheticides again directed attention to the pharmacology of this drug Most of the work is concerned with the rate of absorption and excretion of the various bismuth preparations (chiefly the soluble ones given intramuscularly) An excellent review of this subject is that of von Oettingen<sup>19</sup> A majority of those infrequent dermatoses following the intramuscular injections of bismuth salts are reported in the French literature Erythroderma and scarlatiniform, hemorrhagic, urticarial and exfoliative lesions have been described Less frequently herpes zoster and lesions resembling erythema multiforme occurred, while chronic forms resembled eczematous and maculosquamous eruptions Exfoliative lesions are reported frequently, but the concomitant use of arsenical compounds divides the blame Skolnik and Aleshire,<sup>20</sup> working in a large clinic, found only twenty-two cases of dermatitis caused by bismuth after a three year study during which more than 25,000 intramuscular injections of bismuth had been given The lesions they observed regressed to normal on the abstinence from further treatment, only to reappear when the injections were resumed The acute lesions in general resembled pityriasis rosea, while the chronic ones simulated lichenified dermatitis These

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15 Cabot, R C Bismuth Poisoning, with a Report of a Case, *Tr A Am Physicians* **27** 457, 1912

16 Warfield, L M Bismuth Poisoning, *Am J M Sc* **144** 647, 1912

17 Mayer, L, and Baehr, G Bismuth Poisoning, *Surg, Gynec & Obst* **15**. 309, 1912

18 Morison, R The Treatment of Infective Suppurative War Wounds, *Brit J Surg* **4** 659, 1917 Phillips, J Bismuth Poisoning and Nitrite Poisoning from the Use of Bismuth Subnitrate with a Report of Three Cases, *Cleveland M J* **16** 419, 1917 Hepworth, F A Toxic Symptoms After the Use of Bismuth Paste, *Lancet* **1** 573, 1917 Blight, F J Bismuth Poisoning as Affecting the Oral Cavity, *Brit Dent J* **38** 940, 1917 Wheeler, W I de C Pigmentation from Bismuth Absorption After the Use of B I P P (Bismuth Iodoform Paraffin Paste), *Brit J Surg* **18** 329 (Oct) 1930 Goadby<sup>3a</sup>

19 von Oettingen, W F The Absorption, Distribution and Excretion of Bismuth, *Physiol Rev* **10** 221 (April) 1930

20 Skolnik, E A, and Aleshire, I Skin Eruptions from Bismuth Therapy in Syphilis, *J A M A* **98** 1798 (May 21) 1932

closely resembled those blotchy macular eruptions that had been noted occasionally after the use of dusting powders containing bismuth<sup>21</sup> Several years ago we observed a tabetic patient in ward 15 of the Cook County Hospital who had a deep blue discoloration of the entire oral mucosa after intensive intramuscular bismuth medication Despite this treatment a Charcot knee slowly developed

A variety of animals have been used to study the poisonous effects of bismuth salts Steinfeld and Meyer<sup>22</sup> in their study of the toxicity of subcutaneous injections of bismuth oxide in frogs, cats, rabbits and dogs found two kinds of reaction Acute poisoning characterized by rapid respiration, bradycardia, convulsions and death was seen after a few hours Chronic intoxication was manifest by stomatitis, salivation, diarrhea, anorexia, necrosis and ulceration of the colon Many have reported similar results after the injection of bismuth compounds, whereas oral administration was presumed to be nontoxic Susceptibility varied Dogs and rabbits tolerated large amounts, while cats were poisoned by small doses of bismuth subnitrate<sup>23</sup> Dalche, however, first described the bismuth line<sup>24</sup> He mentioned a brown glistening line on the gums of the anterior molars and the inferior maxilla, with dark violet spots in the mucosa of the left cheek

The first attempt to demonstrate the presence of bismuth in an animal poisoned by its salts by the use of microchemical methods was made by Schmelzer<sup>25</sup> The results were not conclusive Since then bismuth has been isolated from practically every organ of the body, except the skin, of poisoned rabbits<sup>26</sup> and human beings<sup>27</sup> The kidneys, liver and lungs seem to harbor the largest amounts

Most of the work on the absorption of bismuth has been done after intramuscular or intravenous injections, however, Barga, Osterberg

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21 Dorn, L W Ueber Dermatolvergiftung, Beitr z klin Chr **70** 155, 1910  
Windrath Ueber Wismut-Intoxikation Nebst Mitteilung eines todlich verlaufenden Falles nach Application einer Bi-Salbe, Med Klin **6** 742 (May 8) 1910

22 Steinfeld, W, and Meyer, H Untersuchungen uber die toxischen und therapeutischen Wirkungen des Wismuts, Arch f exper Path u Pharmacol **20** 40, 1885

23 Nowak, J, and Gutig, C Nitritvergiftung durch Bismuth subnitricum, Berl klin Wchnschr **45** 1764, 1908

24 Dalche, P, and Villejean, E Recherches experimentales sur la toxicite du bismuth, Arch gen de med **2** 129, 1887

25 Schmelzer, W Studie uber den pathologisch-anatomischen Befund bei der Wismutvergiftung, Jurjew, Schnakenburg, 1896

26 Leonard, C S Tissue Distribution of Bismuth, J Pharm & Exper Therap **34** 333, 1928

27 Munch, J Wismuthvergiftung mit todlichen Ausgang, Dermat Wchnschr **84** 367, 1927 Mayer and Baehr<sup>17</sup>

and Mann<sup>28</sup> found that soluble bismuth salts were readily absorbed by the colon. There is ample evidence to show that bismuth is circulated through the body and that the intensity of excretion is determined chiefly by the concentration of the plasma<sup>29</sup>. Single doses are easily absorbed and excreted, but after successive doses there seems to be a delay in its excretion<sup>30</sup>. In fact, after intensive medication the accumulation of bismuth supervenes.

Only the insoluble bismuth salts were used in our case. There are two possible explanations for the observed pigmentation. Either these salts had been ingested over an unusually long period of time (eighteen years) or the chronic ulceration of the colon had altered the rate of absorption. It is assumed that the prolonged use of the salts caused an excessive accumulation of bismuth in the blood plasma and its deposition in the tissues of the body in a fairly insoluble form, much as occurs in argyria.

Pigmentation of the mucous membranes of the mouth and tongue has frequently been described. A Leitz capillary microscope has been used to study the histopathologic characteristics of the deposits<sup>31</sup>. A similar discoloration has been observed in the urinary bladder of a patient receiving a course of bismuth as a part of his antisyphilitic treatment<sup>32</sup>. Our sections show microscopic features identical with these. Melanosis coli following the use of bismuth has almost the same microscopic picture. It is interesting to note that in two of the three cases of this condition described by Micseh<sup>33</sup> it was associated with pulmonary tuberculosis, as in our case.

A rough though inaccurate estimate of the amount of bismuth in the skin of the entire body was made by means of the Du Bois table for surface area. The skin used in our biopsy was taken from one of the lightest areas, on the basis of its analysis about 82 mg. of bismuth was calculated to have been present in the entire skin.

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28 Bargaen, J. A., Osterberg, A. E., and Mann, F. C. Absorption and Excretion of Arsenic, Bismuth and Mercury. Experimental Work on the Colon, *Am J Physiol* **89** 640, 1929.

29 Sollmann, T., Cole, H. N., and Henderson, K. I. Excretion of Bismuth in a Series of Clinical Bismuth Treatments, *Arch Dermat & Syph* **28** 615 (Nov) 1933.

30 Hanzlik, P. J., and Mehrrens, H. G. Comparative Excretion and Absorption of Different Bismuth Products. Summary Reports, *Arch Dermat & Syph* **22** 861 (Nov) 1930.

31 Lohe, H., and Rosenfeld, H. Untersuchungen über Wismutsaum und seiner Beziehungen zum Gesamtorganismus, *Dermat Ztschr* **50** 409, 1927.

32 Lohe, H., and Rosenfeld, H. Wismuthpigmentierungen der Blasenschleimhaut, *Dermat Ztschr* **57** 250, 1929.

33 Micseh, G. Wismuth Melanose der Dickdarmschleimhaut, *Beitr z path Anat u z allg Path* **92** 147, 1933.

## SUMMARY

A case of generalized permanent discoloration of the skin resembling argyria is reported. The condition developed after the prolonged oral administration of bismuth salts. A method of chemical estimation of the amount of bismuth in the skin is described. The toxicology of bismuth salts is discussed briefly.

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# TULAREMIC PNEUMONIA, PERICARDITIS AND ULCERATIVE STOMATITIS

S B PESSIN, M D

MADISON, WIS

The mortality rate in 3,653 cases of tularemia reported in the United States up to 1933, according to Francis,<sup>1</sup> was 4.9 per cent. Simpson<sup>2</sup> in 1928 stated that the mortality rate in the United States was 3.7 per cent, but Foshay<sup>3</sup> expressed the belief that it is between 6 and 7 per cent. The records of Francis reveal that there are only three states, Connecticut, Maine and Vermont, in which cases of the disease have not been reported. Tularemia is prevalent in Japan and Russia. The occurrence of the disease has recently been reported in Canada, Norway, Sweden and Finland. In England tularemia has occurred only among laboratory workers. Thus, contrary to the general opinion, tularemia, among the infectious diseases, has a relatively high mortality rate and is rather widespread.

Although the literature concerning tularemia is rapidly increasing, there remains much to be elucidated. The causative organism is poorly understood, its disseminating propensities within the human body are not clear, the few descriptions of the histopathologic picture are apparently incomplete and contradictory, and the very promising specific therapy discovered by Foshay has not been given the deserved attention. Thus, three fields, bacteriology, pathology and specific therapy, beckon the investigator toward further exploration. Nevertheless, comparatively few investigators have undertaken the study of this disease. This is proved by the fact that after approximately twenty years of observation of the disease in man specific antiserum "escaped the usual trials" until Foshay<sup>4</sup> introduced it in 1932. *Bacterium tularense* has been known for twenty-five years, yet the motility of this organism has only recently been observed by Ohara<sup>5</sup> and with uncertainty by me. The

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1 Francis, E. Tularemia, *Am J Nursing* **34** 1, 1934

2 Simpson, W. M. Tularemia (Francis Disease), *Ann Int Med* **1** 1007, 1928

3 Foshay, Lee. Personal communication to the author, 1935

4 Foshay, Lee. Serum Treatment of Tularemia, *J A M A* **98** 552 (Feb 13) 1932, Tularemia Treated by a New Specific Antiserum, *Am J M Sc* **187** 235, 1934, On the Treatment of Tularemia, *Ohio State M J* **31** 21, 1935

5 Ohara, cited by Foshay<sup>3</sup>

task of elucidating the histopathologic picture of tularemia is difficult because the necropsy material is deplorably meager and widely scattered. No comprehensive study has been published. Necropsy has been performed in less than 10 per cent of the fatal cases of tularemia. Gundry and Warner<sup>6</sup> in 1934 summarized the results of necropsy in all cases reported in this country, including their own (the fifteenth case). They purposely omitted Breucken's case, reported by Francis and Callender,<sup>7</sup> because the patient died of streptococcic septicemia about five months after the onset of tularemia. They failed to include the cases of Haizlip and O'Neil,<sup>8</sup> Gudger,<sup>9</sup> and Hartman, Beaver and Green.<sup>10</sup> Beck and Merkel<sup>11</sup> reported a case in 1935. Thus 20 cases of tularemia in which necropsy was performed have been reported in this country at the time this paper is written.

The purpose of this presentation is to stimulate physicians to make more postmortem observations in fatal cases of tularemia and to report the clinical and postmortem studies in unusual cases. It must be emphasized that if the present knowledge of the pathologic process of tularemia is to be improved it will be necessary to increase the present percentage of necropsies that are performed in fatal cases. Foshay and others are anxious for all fatal cases to be reported in the literature. I urge those who have studied this disease post mortem to submit their studies for publication.

The following case is the twenty-first reported in this country. It is perhaps the first case of tularemic pneumonia associated with tularemic pericarditis, ulcerative stomatitis and ulcerative glossitis observed at necropsy.

#### REPORT OF A CASE

J. S., a white woman aged 55, entered St. Mary's Hospital on Aug. 15, 1933, with a condition thought to be typhoid. Her chief complaints were severe diarrhea, severe pain in the abdominal region and fever.

She had been camping in the northern part of Wisconsin, along the bank of Lake Superior, two weeks prior to hospitalization. She attributed her illness to

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6 Gundry, L. P., and Warner, C. G. Fatal Tularemia. Review of Autopsied Cases with Report of a Fatal Case, *Ann Int Med* **7** 837, 1934.

7 Francis, E., and Callender, G. R. Tularemia. Microscopic Changes of the Lesions in Man, *Arch Path* **3** 577 (April) 1927.

8 Haizlip, J. O., and O'Neil, A. E. A Case of Meningitis Due to Bacterium *Tularensis*, *J A M A* **97** 704 (Sept 5) 1931.

9 Gudger, J. R. Tularemic Pneumonia. Report of a Case, *J A M A* **101** 1148 (Oct 7) 1933.

10 Hartman, H. R., Beaver, A. C., and Green, R. G. The Occurrence of Tularemia in Minnesota in 1921. Report of Two Cases—One Fatal with Necropsy Report, *Minnesota Med* **16** 559, 1933.

11 Beck, H. G., and Merkel, W. C. Personal communication to the author, 1935.

drinking water from shallow wells and surface springs. While picking blueberries during the first day of camping, she was bitten two times on the right cheek by deer flies, and the following morning she removed three wood ticks from her legs. The areas bitten by the deer flies became swollen and angry red, and suppuration occurred. These areas healed rapidly without leaving a trace of their existence. The bites of the wood ticks caused no noticeable lesions. Two or three days later the patient felt weak and "feverish," and marked diarrhea developed. Thinking that she was afflicted with typhoid as a consequence of drinking surface water, she terminated her vacation and returned home. The temperature during the seven or eight days prior to hospitalization varied from 99 to 100 F in the morning and from 103 to 104 F in the afternoon.

The patient's temperature on her admission to the hospital (6 p m) was 104.2 F, the pulse rate 96 and the respiratory rate 26. Physical examination revealed no lesions on the external surface of the body. Several small grayish-white areas were present on the anterior two thirds of the dorsum of the tongue and on the mucosa of the right side of the lower gum. The abdomen was distended but not rigid, however, there were slight tenderness and definite muscular spasm in the entire right side of the anterior abdominal wall. There were no other positive physical signs. On the following day a trace of albumin was found in the urine. Examination of the blood revealed a normal chemical picture and 4,530,000 erythrocytes, 12,300 leukocytes and 82 per cent neutrophils, which showed a marked shift to the left and a toxic phase plus III. Nothing of note was found in the liquid feces, and the reaction to the benzidine test was negative. The blood serum did not agglutinate *Bacillus typhosus*, *Bacillus paratyphosus*, *Brucella abortus* and *Bacterium tularensis*.

On August 17 the diarrhea subsided. A severe cough developed with expectoration. The tongue appeared dry and contained a few small grayish ulcers.

Small grayish-red ulcers were also present on the gums and on the mucosa of the right cheek. The heart tones were weak and the pulse rate was 115 and irregular and feeble. Moist rales were heard over all pulmonary areas, but they were more pronounced over the upper lobe of the left lung. The abdomen was slightly distended and was rigid and painful below the sternum. The blood culture and agglutination tests were negative.

On August 18 pericardial friction rubs were elicited, the pulse was normal and the temperature was 104 F. The sputum contained many epithelial cells, polymorphonuclear and lymphocytic leukocytes, pneumococci, staphylococci and very small coccoid gram-negative bacilli, no acid-fast bacilli were found.

On August 19 the patient coughed considerably. The expectorations were blood-streaked. She complained of severe pain in the area of the stomach and gall-bladder. Dulness and diminished breath sounds had developed over the upper part of the left lung. Loud friction rubs were heard over the cardiac area. The white cell count was 17,500. A blood culture and agglutination tests were negative.

On August 21 a flat roentgenogram of the chest showed the upper lobe of the left lung to be completely consolidated, and there were scattered consolidations throughout the lower lobe of the left lung (fig 1).

On August 23 ascites developed. The veins of both lower extremities were dilated.

On August 26 a blood culture and agglutination tests were negative.

On August 30 (seventy-three days after the onset of the illness, including eight days of fever at home) the blood serum agglutinated *Bact tularensis* in a dilution of 1:320. Anemia and a slight degree of jaundice had been gradually developed. The erythrocytes numbered 3,290,000. A blood transfusion was performed.



On September 2 the patient's condition became critical. There was a persistent pronounced pericardial friction rub. The temperature was 103 F, the respiratory rate 40 and the pulse rate 128. Oxygen was given by a nasal catheter. Since admission the fever had been of the type noted in cases of typhoid.

After oxygen therapy was instituted, there was a break in the fever, so that by September 8 the temperature was 98 F, and during the following thirty-three days of life it remained between 97.8 and 98.8 F. Leukocytosis persisted with counts between 13,700 and 18,100. At times the patient seemed improved, but never enough to cause doubt as to the gravity of the prognosis. On various days she complained of soreness of the mouth, particularly of the tongue, pains in the abdominal region and dyspnea. She vomited several times. The ulcerations in the mouth remained the same. She coughed persistently, the expectorations decreased, and during the last ten days of life the cough was dry and very distressing. A flat roentgenogram of the chest made at the bedside revealed a

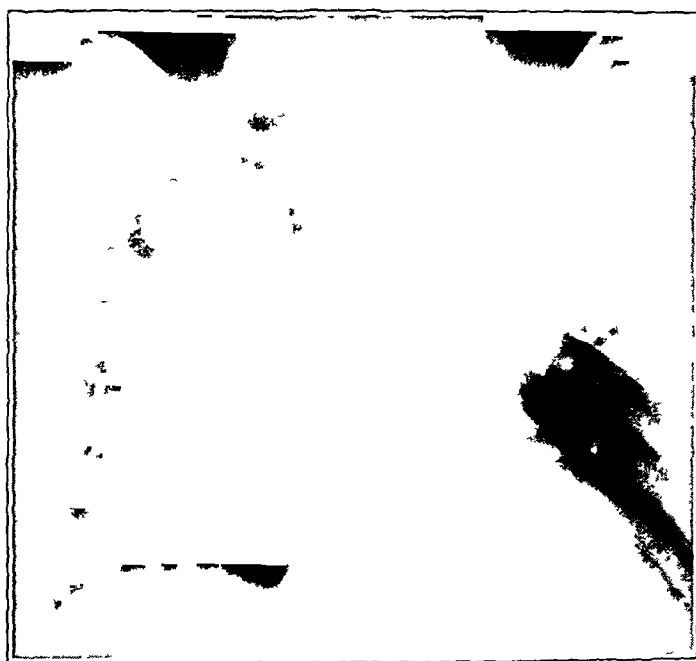


Fig 1—Roentgenogram showing consolidation of the upper lobe of the left lung

marked pericardial effusion and pneumonia of the upper lobe of the left lung associated with effusion (fig 2). Three hundred cubic centimeters of serosanguineous fluid was aspirated from the left side of the chest twelve hours before death. Death occurred on October 9, on the fifty-sixth day of hospitalization and sixty-four days after the onset of the illness.

The blood serum did not agglutinate *Bact tularensis* until the twenty-third day of the illness. Prior to the report of agglutination, the following clinical diagnoses were considered as the disease progressed: (1) typhoid, (2) acute cholecystitis, (3) pneumonia with pericarditis, (4) abscess of the lung, (5) miliary tuberculosis and (6) tularemic pneumonia.

The outstanding unusual manifestations in this case were as follows: (1) severe pains in the abdominal region, with diarrhea, (2) fever of the type present

in typhoid during the first thirty-six days of the illness, with a slow pulse rate, (3) normal and subnormal temperature during the last twenty-eight days of life, as shown in the temperature chart, (4) no lesions on the external surface of the body, (5) persistent leukocytosis and a constant pronounced shift to the left of the neutrophils, (6) mild jaundice, (7) lobar pneumonia with effusion, (8) pericarditis with effusion, (9) ulcerative stomatitis and ulcerative glossitis, (10) mild ascites, and (11) an increasing agglutination titer, which was suggestive on the twenty-first day, 1 320 on the twenty-third day and 1 5,120 on the sixty-fourth day

*Synopsis of Necropsy*—The skin and conjunctiva showed grade 1 icterus. The external surface of the body contained no gross lesions. There was no palpable lymphadenopathy. The mouth was dry. The dorsal surface of the anterior two thirds of the tongue contained several grayish-red shallow ulcers ranging from 0.5 cm in diameter to 2 by 1.5 cm. The lower gum was also ulcerated and presented dirty gray accumulations at the alveolar borders. The



Fig 2—Roentgenogram showing pericardial effusion and pneumonia with effusion

gum of the right side was very edematous. The mucosa of the right cheek was slightly edematous and contained three small grayish-white ulcerated areas. The subcutaneous veins of the anterior thoracic and abdominal walls were prominent and dilated. The right lower extremity below the knee had a grade 2 edema.

The rectus abdominis muscles contained brownish and light grayish-yellow areas. The abdominal cavity contained 550 cc of unchanged serous fluid. The left pleural sac contained 2,100 cc of serofibrinosanguineous exudate, and the right contained 500 cc of similar but less fibrinous exudate. The mediastinal lymph nodes were massive, soft and edematous, and when they were sectioned some contained abscesses composed of a greenish-gray purulent exudate whereas others were involved with conglomerated areas of caseous necrosis. The pericardial sac was enormously dilated, measuring 18 cm at the base and 17.5 cm from the apex to the base. The pericardial sac contained 1,650 cc of serosanguineous

exudate The inner surface of the parietal pericardium and the epicardium were coated with thick ragged fibrinous membranes (fig 4) The surface underneath the fibrinous layers was hyperemic The heart measured 12 cm at the base, and 11 cm from the apex to the base The right auricle and the right ventricle were dilated and filled with fluid and clotted blood The myocardium was brownish red and contained grayish and yellowish areas It was rather flabby but firm The tracheobronchial lymph nodes showed changes similar to those seen in the mediastinum Two of the lymph nodes containing abscesses were 3 cm in diameter The pleura of the left lung was coated with ragged grayish-yellow fibrinous membranes The upper lobe was consolidated in its upper half, and various-sized nodules were felt in the lower half The lower lobe was partly atelectatic The visceral pleura overlying the consolidated portions stripped with ease, displaying yellowish-gray firm elevations and intervening depressed anemic pulmonary tissue When the upper lobe was sectioned confluent lobular caseous pneumonia was seen

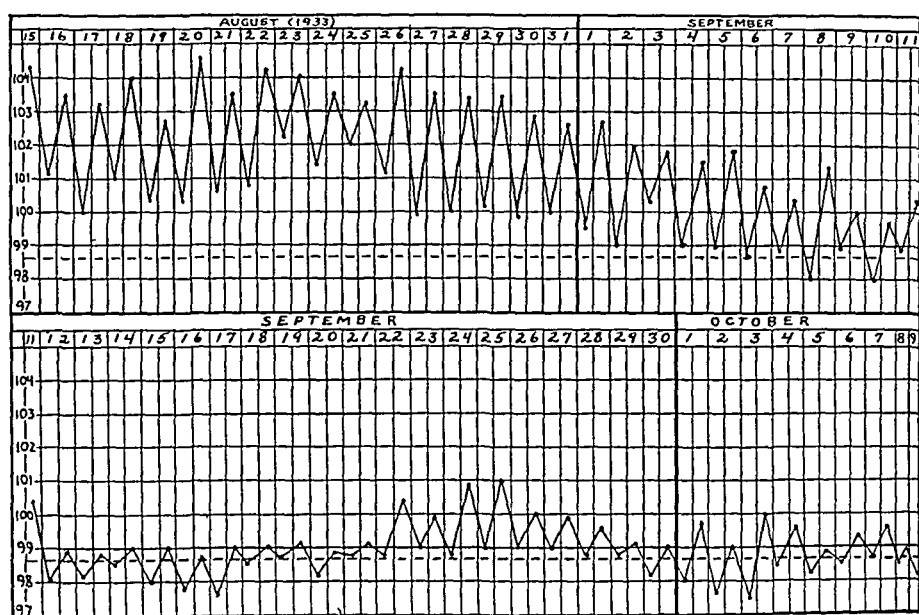


Fig 3—An unusual temperature record

to involve the upper half, and the remaining half contained isolated and conglomerated tubercles ranging in size from 1 mm to 1 cm (fig 5) The intervening pulmonary tissue in the areas of consolidation in the upper half of the upper lobe were depressed The large area of confluent caseous consolidation closely resembled the changes seen in caseous tuberculous pneumonia and was quite unlike the appearance of gray hepatization in croupous pneumonia The surfaces made by sectioning the lower lobe were dry, congested and atelectatic, and an occasional minute tubercle could be discerned The upper lobe of the right lung was emphysematous, and the surfaces made by sectioning were dry and pale The middle lobe contained two large hemorrhagic infarcts and thrombosis of the larger vessels The spleen measured 13.5 by 8.5 by 4.5 cm and weighed 210 Gm The diaphragmatic surface was coated with a thin layer of fibrin Occasional yellowish-white areas were seen through the capsule The pulp was grayish red and contained many foci of caseous necrosis ranging from 2 to 12 mm in diameter (fig 6) The liver measured 26.5 by 19.5 by 9 cm and weighed 1,660 Gm Minute yellow-

ish-white circular foci were seen through the capsule. Some of these were elevated above the surface. Similar nodules, from 1 to 3 mm in diameter, were sparsely scattered throughout the parenchyma. The cortex of the left adrenal gland contained two small yellowish-white circular foci of necrosis. The lymph nodes in the region of the epiploic foramen and the pancreatic, mesenteric, para-aortic and right iliac lymph nodes were large and edematous, and some contained areas of caseous necrosis. The anatomic diagnosis was caseous pneumonia of the upper half of the upper lobe of the left lung with miliary tubercles in the remaining part of the lung, multiple hemorrhagic infarcts and intrapulmonary thrombosis of the middle and upper lobes of the right lung, bilateral fibrinous pleuritis with serofibrinosanguineous effusion, fibrinous pericarditis with serofibrinosanguineous effu-



Fig 4—The upper (greater) half is the inner surface of the pericardium posteriorly, and the lower (lesser) half is the posterior surface of the heart. These surfaces show thick shaggy fibrinous membranes.

sion, multiple foci of caseous necrosis in liver, spleen and left adrenal gland, caseous and suppurative lymphadenopathy of the mediastinal, tracheobronchial, epiploic, gastric, pancreatic, mesenteric, para-aortic and right iliac lymph nodes, ulcerative stomatitis and glossitis, cloudy swelling and fatty changes of the myocardium, Zenker's degeneration of the rectus abdominis muscles, cloudy swelling of the kidneys, and fibrinous perisplenitis. Tularemic pneumonia with pericarditis was considered the cause of death.

*Results of Laboratory Tests*—Separate samples of blood and pleural, pericardial and ascitic fluids were removed post mortem. The blood serum and the pleural and pericardial fluids agglutinated *Bact tularensis* in dilutions up to 1:5,120. The

ascitic fluid in a dilution of 1:80 agglutinated the organism. Two rabbits, one inoculated with pleural exudate and the other with pericardial exudate, died a few hours apart on the fourth day, and the typical miliary lesions of tularemia developed in each. A guinea-pig inoculated with ascitic fluid died of peritonitis on the twentieth day. Triturated tissue from the lungs and lymph nodes and treated centrifugated exudates were cultured for *Bacillus tuberculosis*. The culture mediums remained sterile. Acid-fast stains of smears from caseous material did not reveal any tubercle bacilli.

*Microscopic Examination*—The microscopic observations will be described briefly. A detailed report of the pathologic process of tularemia is being planned.

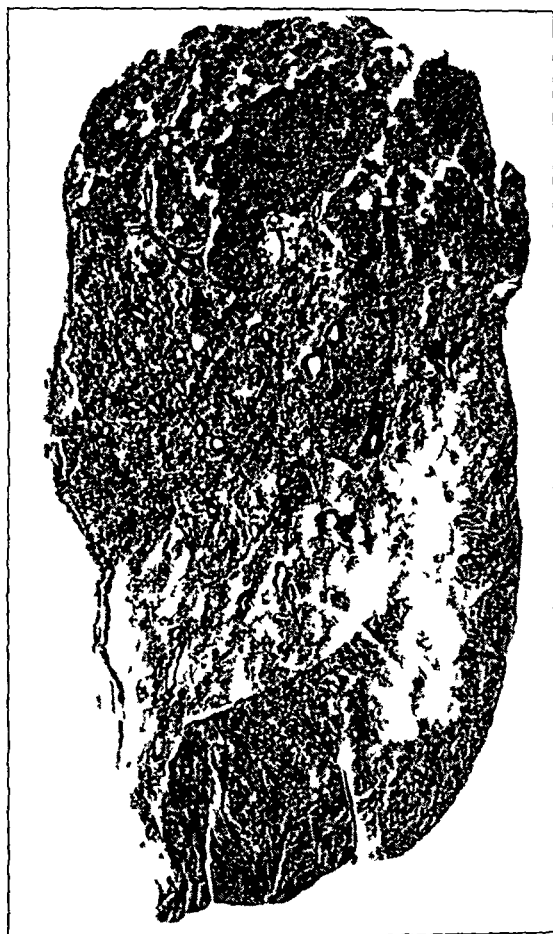


Fig. 5—The upper lobe of the left lung, showing tularememic pneumonia. Discrete tubercles may be seen in the lower half.

Superficially the ulcers of the tongue (fig. 7) and the mucosa of the left cheek were coated with a thin layer of fibrin, which was mixed with cellular debris. Many polymorphonuclear leukocytes and a few lymphocytes, plasma cells and various monocytes with vacuolated cytoplasm were present immediately beneath the fibrinous layer. The polymorphonuclear cells gradually diminished in number as one approached the deeper portions, so that finally the plasma cells and lymphocytes became the predominating elements. Here, polymorphonuclear cells were scanty. Here, also, because of the lessened cellularity, one could quite definitely distinguish fibroblasts, histiocytes and endothelial cells. The cytoplasm of the

endothelial cells was vacuolated. No areas of caseous necrosis were present. Necrosis was limited to the superficial portions of the ulcer. A few macrophages were encountered which, when stained with Foshay's method, showed very small coccobacillary micro-organisms. The bacteria stained poorly and could not be shown satisfactorily in photomicrographs. Gram stains revealed a few gram-positive cocci on the surfaces of the ulcers.

The mediastinal and tracheobronchial lymph nodes showed areas of massive caseous necrosis. Almost the entire tissue was composed of caseous granular acellular material which stained with eosin. A thin rim of lymphoid tissue remained between the capsule and the periphery of the caseous masses. Fibroblasts and epithelioid cells were sparingly and rather evenly distributed in the necrotic



Fig. 6—Largest caseous areas in the spleen

periphery immediately beneath the rim of lymphocytes. A few of these cells mingled with the lymphocytes. Many of the fibroblasts and epithelioid cells were markedly elongated and arranged parallel to each other and perpendicular to the circumference of the caseous material. The reticulum fibers along the periphery were thickened. They appeared to be increased in amount and disappeared in the caseous material. A few of the nodes of the mediastinum were extensively infiltrated with polymorphonuclear neutrophils, but there was no caseation. The abdominal lymph nodes showed marked destruction of the normal architecture, and various-sized caseous foci were present in all the sections. The peripheries of the caseous areas were much more cellular than those of the thoracic lymph nodes. Occasional giant cells of the Langhans type were encountered. The marked similarity of these lesions to those of caseous tuberculosis prompted an examination

with acid-fat stains. No acid-fast bacilli were found. Minute rods were found in the necrotic areas and epithelioid cells in the sections stained by Foshay's method.

Sections of the large consolidated mass in the lungs showed merely an acellular caseous material in which there were a few aggregations of cellular debris. No vital cells were encountered. Sections from the periphery of the caseated consolidation revealed a confluence of caseous areas (fig 8). The periphery of the necrotic areas were either acellular or scanty cellular or contained thin rims of densely packed cells. The alveoli between the irregular caseous expansions contained monocytes and a pinkish colloid-like-staining material which was homogeneous, like that present in the lumens of the blood vessels, vacuolated, or vacuolated and granular. This colloid-like material, which undoubtedly was serum, contained no threads of fibrin. The monocytes were large and contained relatively small nuclei and a large amount of clear vacuolated cytoplasm. They were undergoing extensive fatty metamorphosis and showed various stages of degeneration. The cytoplasm of a few of the monocytes contained hemosiderin and



Fig 7—Photomicrograph of a section of a tularemic ulcer of the tongue

anthracotic granules. These monocytes were endothelial leukocytes and desquamated alveolar epithelial cells. The majority appeared to be alveolar epithelial cells. The sequence of the pathologic process was studied from sections taken some distance from the area of caseous consolidation, where small caseous foci were scattered discretely. Apparently, the early reaction consisted of edema of the alveolar wall, swelling of the endothelium of the capillaries, swelling of the alveolar epithelial cells and infiltration of the alveolar wall with lymphocytes and polymorphonuclear leukocytes. Serum without or with a few cells exuded into the alveolar spaces. The alveolar epithelium became swollen and dropped into the serous fluid. Endothelial leukocytes also migrated into the alveolar spaces. Some alveolar spaces were completely filled with closely packed monocytes, whereas others merely contained serous exudate without cells or with few cells. A few other cells, such as lymphocytes, polymorphonuclear neutrophils, plasma cells and eosinophils, were observed in the alveolar spaces, these cells were limited to the alveolar walls and lobular septums and occurred around larger blood vessels and

in the peribronchial connective tissue. In some areas the plasma cells predominated, whereas in other areas the majority of the cells were lymphocytes. The process of necrosis and its usual site of origin were not definitely determined. The necrosis seemed to originate in the alveolar wall or from the serous exudate mixed with mononuclear cells. This problem awaits further study. It was apparent that necrosis did not begin within the blood vessels or around the blood vessels, bronchiolar walls or peribronchial connective tissue. These structures usually suffered destruction when they became incorporated with the advancing necrosis. According to the appearance of the discrete caseous foci, it seemed apparent that in the lung at least the macrophagic response was weak. Very few cellular elements surrounded the periphery of the lesion. There was, however, an attempt to dispose of the deleterious material, and this was evident by the strenuous ameboid efforts of monocytes to penetrate the depths of the necrotic tissue. However, these monocytes apparently were soon destroyed. Some of the monocytic cells were undoubtedly fibroblasts, because they were intimately associated with the few collagenous fibers at the periphery of the caseous areas. Other monocytes resembled epithelioid cells. Poorly formed giant cells of the Langhans type were occasionally encountered at the periphery of a caseous area. The lumens of the small bronchi and bronchioles were filled with necrotic or caseous material. Some of the respiratory tubes, although filled with necrotic material, were perfectly intact and well preserved (fig 8), others were partially necrotic, and still others were completely necrosed. Thrombosis of the blood vessels was not observed in the left lung. The right lung contained many thrombosed vessels and a few hemorrhagic infarcts, yet this lung was free from tularemic lesions.

There were many small round discrete and large confluent stellate and septate caseous areas in the spleen. Two distinct cellular zones encircled the necrotic, almost acellular material. The inner zone was composed of a scanty, cellular, rather thick layer of ovoid and markedly elongated monocytes mingled with thick strands of collagenous fibers. The strands were definitely continuous with the spindle-form cells. Other monocytes consisted of relatively large, light-staining ovoid nuclei, some of which were indented and recognized as epithelioid cells. A third group of monocytes contained relatively small round or ovoid light-staining nuclei and a large amount of clear cytoplasm undergoing a fatty metamorphosis, these cells were recognized as endothelial cells. The outer zone was cellular and consisted of plasma cells and lymphocytes with a few monocytes and occasional eosinophils. Few polymorphonuclear leukocytes were present in either of the two distinct layers. A few polymorphonuclear leukocytes were found in the caseous material. The peripheries of some of the caseous tubercles occasionally showed hemorrhagic infiltration. Areas of extreme congestion with deposits of abundant hemosiderin were everywhere observed. Giant cells were occasionally encountered.

In the liver the caseous tubercles were all found immediately beneath the capsule (fig 9). None were observed more than 1 mm beyond the capsule. They were contiguous with the capsule, or a small layer of liver cells intervened. The caseous foci ranged between 0.5 and 2.5 mm in diameter and in construction were essentially similar to those of the spleen. Only two giant cells were found in the thirty-five tubercles that were studied. Hemorrhage around the periphery of the tubercles was more frequent in the liver (fig 9) than in the spleen. Moderate acute hepatitis was present, with rather marked fatty and granular changes of the hepatic cells. The polymorphonuclear infiltration was both central and peripheral, with the intervening liver cells free from leukocytic infiltration. Many of the hepatic cells were filled with bile pigment. The portal areas were infiltrated with



lymphocytes and appeared well preserved. The lumens of several central veins were filled with white thrombi. The parenchyma was congested, and occasionally a small hemorrhage was observed.

The epicardium was coated with a thick layer of acellular fibrin, beneath which a vigorous organization was present. The chief cellular elements in the organizing tissue were lymphocytes, plasma cells and fibroblasts. Numerous capillaries were present. The epicardium was thick, and both the epicardium and the subepicardial tissue were infiltrated with cellular elements similar to those in the organization previously described. The myocardium showed marked granular and fatty changes. No caseous necrosis was observed.

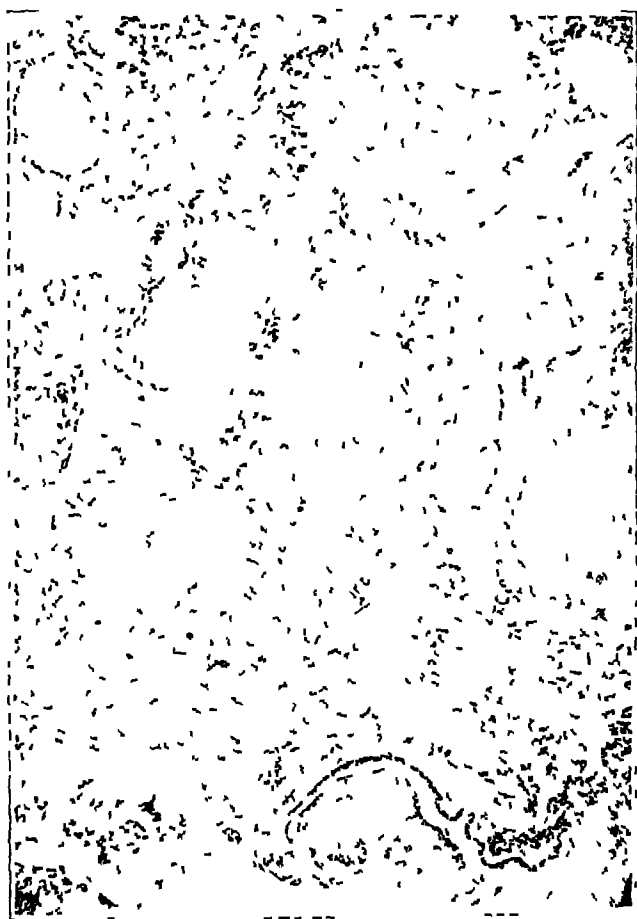


Fig 8—Photomicrograph of a section of the lung, showing confluence of caseous foci.

The cortex of the left adrenal gland contained three discrete areas of caseous necrosis, similar in structure to those seen in the liver.

The right rectus muscle showed Zenker's degeneration. There was a marked cloudy swelling of the tubular epithelial cells of the renal cortex. Many sections of kidney tissue were studied, but no foci of caseous necrosis were seen. *Bact tularensis* was found in the lesions of the lung, spleen, lymph nodes and epicardium. It could not be demonstrated in the liver.

## REVIEW OF CASES IN WHICH NECROPSY WAS PERFORMED

It is rather a curious incident that the postmortem examination in each of the 21 cases thus far recorded in the literature was performed by a different person

Infection occurred in 17 cases from the handling of rabbits, in 2 cases from the bites of deer flies, in 1 case from contact with an opossum and in 1 case from ingestion of the flesh of a rabbit The usual period of incubation was from three to four days A period



Fig 9—Photomicrograph of a subcapsular caseous area of the liver Hemorrhage is seen at the periphery of the lesion

of incubation of less than one day was reported by Permar and Mac-lachlan<sup>12</sup> Their patient, a Negro, became nauseated and fatigued on the evening of the same day on which he cleaned a large number of rabbits, and on the following day he had chills and fever The patient of Bardon and Berdez<sup>13</sup> became acutely ill the day after cutting up

12 Permar, H H, and Mac-lachlan, W W G Tularemic Pneumonia, *Ann Int Med* 5 687, 1931

13 Bardon, R, and Berdez, G Tularemia Report of a Fatal Case with Postmortem Observations, *J A M A* 90 1369 (April 28) 1928

the carcass of a rabbit. The longest period of incubation (seven days) was encountered in Simpson's<sup>2</sup> case. In 18 cases the condition was of the ulceroglandular type, and in 3 cases, of a typhoid character. According to Beck and Merkel,<sup>11</sup> their case is the only one of the typical typhoid type in which necropsy was performed. Permar and MacLachlan's case was probably an instance of the typhoid type, and in our case the condition was of typhoid character during the first thirty-six days of the sixty-four days of illness. The temperature was usually between 101 and 103 F, but occasionally it rose to 105 F. The leukocyte count varied considerably. In 5 cases it was below 8,000. The lowest leukocyte count, 3,300, was reported by Haizlip and O'Neil, and the highest, 22,600, by Goodpasture and House.<sup>14</sup> Eighteen counts were recorded in our case, the lowest was 11,450 and the highest, 18,100. There was always a marked shift to the left, and the band forms in every differential count exceeded the number of segmented neutrophils. Gundry and Warner give the average of 10,800 for 12 cases. The agglutination tests were positive during the second week and were constantly negative before the eighth or the ninth day. Those that performed agglutination tests more than once found that the titer increased during the course of the disease. The titers in Masee's<sup>15</sup> case were 1:40 on the fifteenth day and 1:320 on the eighteenth day, in Hartman's<sup>16</sup> case, 1:640 and 1:1,280 on the fifteenth and eighteenth days, respectively, in Blackford's<sup>17</sup> case, 1:40 on the ninth day and 1:5,120 on the twenty-fifth day, and in Gudger's<sup>9</sup> case, 1:320 on the sixteenth day and 1:5,600 at the end of the third week. The results of agglutination tests in our case were as follows: nineteenth day, negative, twenty-first day, suspicious, twenty-third day, a titer of 1:320, post-mortem blood and serous exudates on sixty-fourth day, a titer of 1:5,120. Septicemia and pulmonary involvement predominated clinically. Bronchopneumonia was diagnosed in 7 cases, lobar pneumonia in 4, abscess of the lung in 1 and pleural effusion in 2. Other frequent clinical manifestations were nausea and vomiting, abdominal distention and cough (with or without rusty or blood-streaked sputum). Diarrhea was recorded in 4 cases, and in our case it persisted for ten days.

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14 Goodpasture, E. W., and House, S. J. The Pathologic Anatomy of Tularemia in Man, *Am J Path* **4** 213, 1928.

15 Masee, J. C. Tularemia in Georgia. Report of a Case, *J. M. A. Georgia* **20** 66, 1931.

16 Hartman, F. W. Tularemic Encephalitis, *Am J Path* **8** 57, 1932.

17 Blackford, S. D. Pulmonary Lesions in Human Tularemia. Pathologic Review and Report of a Fatal Case, *Ann Int Med* **5** 1421, 1932.

Jaundice occurred twice, in Verbrycke's<sup>18</sup> case and in ours. Marked pericardial friction sounds were present in our case. Death usually occurred within from fourteen to twenty days after the onset of the illness, however, Simpson's patient lived only four days and Palmer and Hansmann's eight days. On the other hand, death occurred much later in 3 cases: forty-one days (Blackford), sixty-four days (our case) and five months (Bruecken, cited by Francis and Callender<sup>7</sup>). Bruecken's patient died of septicemia due to *Streptococcus haemolyticus* and perhaps should not be included in the prognostic summary.

The primary lesion persisted and was found at necropsy in all but 3 cases. Palpable lymphadenopathy was absent in Permar and MacLachlan's case and in ours, however, visceral lymphadenopathy was present in all the cases. Pulmonary lesions were constantly found post mortem. The pathologic changes in the lungs varied, they were described as bronchopneumonia, confluent lobular pneumonia and lobar pneumonia, with or without necrosis or caseation, miliary focal necrosis, abscesses and cavitation and fibrinous pleuritis. Marked pneumonia was present in 10 cases, pleural effusion in 4 and abscess of the lung and cavitation in 2. Areas of necrosis or caseation in the lungs were described in 16 cases. Multiple foci of caseous necrosis were present in the liver 15 times and in the spleen 16 times. Although foci of caseous necrosis are usually present both in the liver and in the spleen, in 3 cases (Francis and Callender, Bunker and Smith<sup>19</sup> and Haizlip and O'Neil) they were absent in the liver and present in the spleen, whereas in 2 other cases (Masse and Permar and MacLachlan) they were present in the liver and absent in the spleen. It is interesting to note that in Simpson's case, in which death occurred four days after the onset, there were multiple caseous foci in the liver and spleen and that in Bruecken's case, in which death occurred about five months after the onset of tularemia, there were also multiple caseous areas in the same organs. Death occurred forty-one days after the onset of the illness in Blackford's case, but no lesions were present in the liver and spleen, whereas in our case, in which the patient died sixty-four days after the onset, many caseous foci were present in those organs. Gudger's patient died thirty-one days after the onset, and no lesions were found in the liver and spleen.

The most common sites of tularemic lesions are therefore the skin, lymph nodes, lungs, liver and spleen. Other tissues and organs are

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18 Verbrycke, J. R., Jr. Tularemia, with Report of a Fatal Case Simulating Choleraeitis, with Postmortem Report, *J. A. M. A.* **82** 1577 (May 17) 1924.

19 Bunker, C. W. O., and Smith, E. E. Tularemia. Report of Four Cases, One Fatal, with Autopsy Report, *U. S. Nav. M. Bull.* **26** 901, 1928.

rarely affected Foulger, Glazer and Foshay,<sup>20</sup> Schumacher<sup>21</sup> and Gundry and Warner found lesions on the peritoneum Hartman<sup>18</sup> and Bryant and Hirsch<sup>22</sup> have convincingly demonstrated lesions in the meninges and brain The adrenal glands in a case of Francis and Callender contained multiple necrotic foci Two caseous foci were noted grossly and three microscopically in the left adrenal gland in our case The kidneys undoubtedly possess a striking resistance against tularemic infection, even in the experimental animals, yet Bardon and Berdez found a few nodules, similar to those of the spleen, in the kidneys of their patient In the unusual and interesting case of Beck and Merkel, ulcers were present in the stomach, duodenum, ileum and cecum Tularemic fibrinous and caseous pericarditis and tularemic ulcerative stomatitis with ulcerative glossitis were present in our case

#### COMMENT

Tularemia can be readily diagnosed when one is confronted with the usual classic history and objective findings However, when the history is vague and recondite and when external lesions are absent, one must conclude that "the most important fact in the diagnosis of tularemia is to have the disease in mind"<sup>23</sup> The unusual and perplexing cases are hailed as the typhoid and pneumonic forms of tularemia We have been strongly influenced by the observations of the ulceroglandular, oculoglandular and glandular types but rather inattentive to the less frequent forms Undoubtedly a surprising number of unusual cases of tularemia have escaped correct diagnosis both by the clinician and by the pathologist Some of the most interesting cases would have eluded recognition if it had not been for the alert clinicians' demands for agglutination tests These cases would also have escaped recognition at postmortem examination because the gross pathologic picture and, according to some investigators, the microscopic pathologic picture are similar to those seen in cases of tuberculosis A few have even insinuated that at necropsy in fatal cases of tularemia the condition has been diagnosed as pulmonary tuberculosis or milary tuberculosis On the other hand, as in our case, it is definitely known that internists,

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20 Foulger, M, Glazer, A M, and Foshay, L Tularemia Report of a Case with Postmortem Observations and a Note on the Staining of Bacterium Tularensis in Tissue Section, J A M A **98** 951 (March 19) 1932

21 Schumacher, H W, cited by Francis, E Symptoms, Diagnosis and Pathology of Tularemia, J A M A **91** 1155 (Oct 20) 1928

22 Bryant, A R, and Hirsch, E F Tularemic Leptomeningitis Report of a Case, Arch Path **12** 917 (Dec) 1931, Tr Chicago Path Soc **14** 9 (June 1) 1932

23 Simpson, W M Tularemia Summary of Recent Researches, Ohio State M J **29** 35, 1933

surgeons and dermatologists have erroneously diagnosed the condition in the fatal cases as influenza, chronic bronchitis, typhoid, septicemia, tuberculosis, an acute abdominal condition, acute cholecystitis, cholelithiasis, cholangitis, pyelitis, peritonitis, syphilis, pustular acne and sporotrichosis. Even the serologist, because of the cross-agglutination of *Bact tularensis* with *Br abortus* and *Br melitensis*, caused tularemia to be diagnosed as undulant fever. The blood serum of the patients of Gudger and of Beck and Merkel agglutinated *B paratyphosus*. Verbrycke's patient, because of jaundice and acute abdominal symptoms, underwent an unnecessary exploratory laparotomy.

Verbrycke's case, the first in which necropsy was reported, is an excellent illustration revealing the importance of an accurate history. The patient and her relatives misunderstood the physician's questions, and the result was that the correct information was not obtained until after the patient died. However, it is not infrequently encountered that the physician is faulty in taking the history. It must be kept in mind that rabbits, flies and ticks, while they are the most frequent source of infection, are not the only purveyors of tularemia. The squirrel, wild rat and mouse, woodchuck, hog, coyote, cat, opossum, grouse and quail have infected man. The guinea-pig has been the source of infection among laboratory workers. The following insects are known to convey the bacillus: rabbit louse, mouse louse, squirrel flea, bedbug and stable fly. Man to man infection has not been observed.

It has been conclusively proved that the portal of entry is not always a wound in the skin. The pioneer workers, Francis, Mayne and Lake, had tularemia without evidence of portal of entry<sup>24</sup>. Simpson has demonstrated that the organism will penetrate the unbroken skin of the guinea-pig. Cases of tularemia without demonstrable lesions have been reported by Francis. The heroic subject Madam Ohara enabled her husband<sup>25</sup> to prove that *Bact tularensis* can penetrate the unbroken skin. She contracted tularemia after Ohara rubbed the myocardium and blood of an infected rabbit on the hairy part of her hand and thumb. That the ingestion of insufficiently cooked rabbit meat produced the disease in seven members of a Negro family was reported by Crawford<sup>26</sup>. Many of Ohara's patients stated that they were poisoned by eating the flesh of rabbits. Permar and MacLachlan suggested the possibility of primary

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24 Simpson, W. M. *Tularemia: History, Pathology, Diagnosis and Treatment*, New York, Paul B. Hoeber, Inc., 1929.

25 Ohara, Hachiro. *Experimental Inoculation of Disease of Wild Rabbits into the Human Body*, Japan M. World **6**: 300, 1926.

26 Crawford, M. *Tularemia from the Ingestion of Insufficiently Cooked Rabbit*, J. A. M. A. **99**: 1497 (Oct. 29) 1932.

infection of the respiratory tract in tularemic pneumonia. It is thus apparent that the unbroken skin and the alimentary and the respiratory tract may be the primary portal of entry.

The various clinical manifestations and necropsy observations indicate that the cause of death varies. Foshay<sup>27</sup> has collected reports of a series of fatal cases, and in a forthcoming paper he intends to elucidate the cause and mode of death and the possibility of preventing death with serum therapy. He has assembled the fatal cases into four groups.

**Group 1** In this group primary bacteremia is followed by fatal septicemia, death occurring within ten days. The patients lack a natural resistance and react as rodents.

**Group 2** This group consists of cases of "tularemic sepsis." Death occurs during the third or fourth week of sickness, the average length of time before death is eighteen days. Primary bacteremia disappears, but secondary bacteremia develops owing to necrosis of blood vessels in caseous foci, as in tuberculosis. Another possible cause for the development of this secondary bacteremia may be the lymphogenous transportation of bacteria into the blood stream after the material drained from infected tissues has emptied into the cisterna chyli, the thoracic duct or the right lymphatic duct. Most of the fatal cases occur in this group.

**Group 3** In the cases in this group tularemic pneumonia predominates clinically, and death is due to intoxication.

**Group 4** In the cases in this group death occurs six weeks or more after a collapse of the immune mechanism or as a result of previous pathologic processes in various organs.

The cases of Simpson and Palmer and Hansmann belong to group 1. According to Foshay, "tularemic sepsis" (group 2) is treacherous and clinically may occur with the mildest infections. Foshay expressed the belief that 1 of every 15 patients will have "tularemic sepsis." He stated that there is no way of predicting its arrival, and that in cases of mild infection it is a dramatic change. Once sepsis has occurred, the patient rarely survives for more than six or seven days.

The duration of the disease is usually comparatively short, and the majority of persons recover. However, the period of convalescence is of comparatively long duration. In a few cases the condition runs a chronic course. Nakada's<sup>28</sup> patient remained in the hospital for seven and one-half months. The duration of the disease and convalescence

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27 Foshay, Lee. Personal communication to the author.

28 Nakada, J. R. Tularemia (Three Cases), *J. Missouri M. A.* 30:120, 1933.

can be considerably shortened and the prognosis rendered entirely favorable by treating the patient with Foshay's antiserum. According to Foshay,<sup>27</sup> not a single fatality occurred in 350 patients treated with antiserum. On the basis of the mortality rate, there should have been 22 deaths in Foshay's group if serum therapy had been omitted. Simpson<sup>29</sup> emphasized the fact that Foshay's antiserum produced a prompt and favorable influence on the fever and lymphadenopathy and stated that when the results in a series of cases in which treatment is administered are compared with those in cases in which no treatment is given, there is "little doubt as to the efficacy and specificity of the treatment."

Since agglutination tests in cases of tularemia are not positive until the second week and in not a few instance until after the second week (twenty-third day in our case), a more rapid diagnostic method should meet with approval. Foshay's skin test (the injection of bacteria killed with formaldehyde and subsequently treated either with a solution of hydrogen peroxide or with nascent nitrous oxide) has proved to be a reliable diagnostic procedure.

The gross pathologic picture in fatal cases is rather characteristic, particularly when multiple small necrotic foci are present in the lungs, liver and kidneys. These lesions may be confused with those seen in miliary tuberculosis.

The histopathologic picture of tularemia will probably be placed in the category of specific inflammations in the near future. At present, the microscopic observations are meager and contradictory. Necrosis in tularemia has been attributed to vascular occlusion. Simpson maintained that vascular occlusion due to thrombosis does not cause caseation. I firmly believe that thrombosis and vascular occlusion result from the spread of necrotization. Patent lumens with fairly well preserved vascular walls in the midst of caseous areas were observed in our case.

#### SUMMARY

The clinical and necropsy studies in a case of tularemic pneumonia with pericarditis and ulcerative stomatitis are presented.

The importance of publishing the results of necropsy in all cases of tularemia is emphasized.

All published reports on necropsies (21 to date) in fatal cases of tularemia are reviewed.

The mode of infection, the clinical course and the diagnostic and therapeutic procedures are discussed.

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29 Simpson, W. M. Personal communication to the author.



## ADDENDUM

For some inexplicable reason I failed to include Kavanaugh's<sup>30</sup> case in the review of all reported cases of tularemia in which necropsy was performed. Kavanaugh's patient had primary ophthalmic tularemia. Death occurred twelve days after the onset. Necropsy revealed fibrinopurulent membranous palpebral conjunctivitis of the right eye, preauricular, superior cervical, submaxillary, mediastinal, hilar, mesenteric and retroperitoneal lymphadenopathy, multiple foci of necrosis in the lungs, liver and spleen, and fibrinopurulent peritonitis. Complete clinical information on this case was not presented, but from the various sections of the paper it was gathered that infection occurred after dressing a wild rabbit and that clinical symptoms of pulmonary involvement and general peritonitis were present. Thus necropsy has been reported in 22 cases of tularemia in this country to date (July 18, 1935).

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30 Kavanaugh, C. H. Tularemia, *Arch Int Med* **55** 61 (Jan) 1935

# LYMPHEDEMA (ELEPHANTIASIS) OF THE EXTREMITIES CAUSED BY INVASION OF LYMPHATIC VESSELS BY CANCER CELLS

## REPORT OF TWO CASES

HAMILTON MONTGOMERY, M D

ROCHESTER, MINN

In the two unusual cases reported here, lymphedema (elephantiasis) of the extremities was the result of malignant invasion of the lymphatic structures. In the first case the condition was caused by a squamous cell epithelioma extending from the left ankle to the groin, and in the second case the cause probably was direct extension of an endothelioma of the pleura to the lymphatic structures of one arm. Lymphedema, or elephantiasis (an advanced stage of lymphedema), of the extremities rather frequently results from metastatic involvement of inguinal or axillary lymph nodes or from surgical removal of lymph nodes, especially those which are involved in cases of carcinoma of the breast. Development of lymphedema as the result of packing of the lymphatic channels of an extremity with tumor cells, thus obstructing the flow, is, I believe, uncommon. The various types of lymphedema of the extremities and their relative frequency of occurrence recently have been reviewed by Allen<sup>1</sup>

## REPORT OF CASES

A farmer aged 56 years was seen in the Mayo Clinic in June 1934, because of swelling of the left leg. Eight years previously a small nodule had appeared on the medial aspect of the left ankle, and shortly thereafter a mass had appeared in the left groin. A physician of the patient's home community had excised from the left ankle a lesion the size of a quarter-dollar (about 2.5 cm in diameter), and from the groin the same physician had removed a large nodule. On the basis of examination of the tissue, a diagnosis had been made of sarcoma of the ankle and of an inflammatory reaction in the left groin. Edema of the ankle gradually had developed and had proceeded up the leg. The patient had received thirteen roentgen treatments without any evidence of improvement. Generalized edema of the leg had been present for four years, but this had not progressed during the year previous to the patient's visit to the clinic. In the course of the four years mentioned, the patient had had four attacks of recurrent lymphangitis and cellulitis associated with chills, fever and nausea and vomiting. Treatment had consisted of local application of heat and ointments to relieve the swelling of the leg. Roent-

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From the Section on Dermatology and Syphilology, The Mayo Clinic

1 Allen, E V. Lymphedema of the Extremities. Classification, Etiology and Differential Diagnosis, a Study of Three Hundred Cases, Arch Int Med 54 606 (Oct) 1934

gen treatment had not been given for five years before the man came to the clinic. He had not lost weight.

Examination revealed an indolent ulcer of the left ankle and marked lymphedema (elephantiasis) of the left leg. In many areas the skin had a verrucous appearance, such as frequently is seen in cases of benign lymphedema (fig 1). The ulcer was indurated, but it lacked a pearly border. Characteristics of squamous cell epithelioma, sarcoma and endothelioma were considered in making the diagnosis. There was no evidence of varicose veins. Extending up the leg were many discrete hard subcutaneous nodules, which apparently followed the course of



Fig 1 (case 1)—Squamous cell epithelioma of the ankle, with resulting elephantiasis

the lymphatic structures. There was no evidence of arsenical pigmentation or of keratosis. There was a large, hard mass, about 12 cm in diameter, in the left iliac fossa. General examination, including roentgenograms of the pelvis and the leg for evidence of involvement of bone, gave essentially negative results. Excision of the inguinal mass revealed a great cluster of lymph nodes, which were fairly soft. Examination of a specimen taken for biopsy disclosed squamous cell epithelioma of grade 2. Involvement of the iliac fossa was too extensive to warrant surgical intervention. Palliative treatment with roentgen rays seemed contraindicated because of the possible danger of increasing the degree of elephantiasis.

*Comment*—This case is of interest from several points of view. An original diagnosis was made of sarcoma of the ankle. In view of the data, however, I am certain that the original lesion was an epithelioma rather than that there was a change from sarcoma in the primary lesion to epithelioma in the metastatic growths which were found in the lymph nodes. I have observed several cases of neoplasm of the extremities in which the histologic picture at first glance suggested sarcoma or even endothelioma but in which, through serial section, it was possible to demonstrate the origin of the tumor cells from the epidermis and in small areas typical prickle cells of a squamous cell epithelioma could be found.

Despite the absence of loss of weight, the malignant character of the ulcer in this case seemed definite. Cases have been reported, however, in which malignant growth was thought to be present but on histologic examination of tissue the condition was found to have resulted from tuberculosis or varicose ulcer. The latter, of course, also may rarely eventuate in epithelioma. The four attacks of recurrent lymphangitis and cellulitis in my case might have suggested an inflammatory basis for the elephantiasis. That lymphangitis and cellulitis may be expected as secondary and contributing factors to elephantiasis is readily understood on the basis, first, of infection of the open ulcer and, second, of the inflammatory reactions associated with epithelioma. Whether roentgen treatment had anything to do with the subsequent increase in elephantiasis is difficult to decide.

In most cases of epithelioma of the extremities elephantiasis, or lymphedema, does not develop. Beck<sup>2</sup> barely referred to elephantiasis associated with epithelioma in these regions. Cesareo de Asis,<sup>3</sup> in a review of a large series of cases of carcinoma (epithelioma) of the lower extremities, did not mention elephantiasis. Conversely, Muller and Jordan,<sup>4</sup> in a review of elephantiasis nostra, did not mention epithelioma as an etiologic factor, nor is this mentioned in recent textbooks on dermatology as a possible cause of elephantiasis. In a recent study<sup>5</sup>

2 Beck, S. C. *Geschwulste der Haut (II) Epithelioma*, in Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1933, vol. 12, p. 208.

3 de Asis, Cesareo. *Cutaneous Carcinoma of the Lower Extremities. A Study of Cases at the Barnes and Barnard Free Skin and Cancer Hospital of St. Louis, Missouri*, *Ann Surg* **83** 663 (May) 1926.

4 Muller, G. P., and Jordan, C. G. *Elephantiasis Nostra*, *Ann Surg* **97** 226 (Feb.) 1933.

5 Montgomery, Hamilton. *Arsenic as an Etiologic Agent in Certain Types of Epithelioma. Differential Diagnosis from, and Further Studies Regarding, Superficial Epitheliomatosis and Bowen's Disease*, *Arch Dermat & Syph* **32** 218 (Aug.) 1935.

of epithelioma, whether the sequel of arsenical keratosis of the palms and soles or independent thereof, none of the patients had associated elephantiasis, nor did I find mention of such an association of conditions in the literature on the subject which I reviewed. Allen<sup>6</sup> found that in 10 per cent of three hundred cases of lymphedema the condition was attributable to malignant occlusion of the lymphatic channels, but in the majority of these cases carcinoma of the breast was an associated condition. In only three cases (1 per cent) did the elephantiasis result from an epithelioma, or a melano-epithelioma, of an extremity, and in each of the three cases the lymphedema developed only after surgical removal of lymph nodes from the groin. Judging from recent articles, the percentage of elephantiasis that is attributable to epithelioma of an extremity is small, but epithelioma always should be considered as a possible etiologic agent.<sup>7</sup>

CASE 2—A basket-weaver aged 52 was seen in the clinic in November 1927, because of swelling of the right arm of six months' duration. Three years previously he had noted a neuritic pain in the right shoulder, which lasted a year before it disappeared. Simultaneously with the swelling of the arm, a red area appeared in the right pectoral region and spread over the abdomen, the flank, the remainder of the thorax and the arm. A history of attacks of erysipelas or cellulitis was not obtained.

Examination revealed definite edema of the whole right arm, which was about one and one-half times the size of the left arm. The right side of the trunk was similarly edematous. In the axilla the skin had a verrucous appearance. The axillary lymph nodes were slightly enlarged. In places, there were thick-walled, vesicle-like elevations, from which, when they were opened, there exuded a watery secretion. Roentgenograms of the thorax gave evidence of rather marked fibrosis. The roentgenologist, who did not know the patient's occupation, asked if he was a miner, because of the type of pulmonary changes. Neurologic examination gave negative results. It was thought that the obstruction of the lymphatic flow came from within and might be the result of obstruction of the right thoracic duct. The differential diagnosis also included the possibility of the presence of tuberculous lymph nodes, with secondary obstruction, hypertrophic lymphangioma and scleroderma. A malignant process was not seriously considered. There was no evidence of a cervical rib.

A specimen for biopsy was taken from about the level of the iliac crests and another from the right flank, a most unusual histologic picture was revealed (fig 2). All the lymph vessels were packed with large mononuclear cells in which were many mitotic figures, and evidence was present also of amitotic cell division. In other cells pyknosis of the nuclei and degenerative changes in the cytoplasm were noted. A few of the tumor cells were seen between connective tissue bundles, but evidence of a malignant lymphangio-endothelioma of the skin, such as has been described by Nather,<sup>8</sup> was not observed. The cells were not sufficiently differ-

6 Allen, E. V. Personal communication to the author.

7 Nobl. Kombinierte Erscheinungsform eines Fersencarcinoms mit tuberöser Elephantiasis, *Zentralbl. f. Haut- u. Geschlechtskr.* **11** 464, 1924.

8 Nather, Karl. Ueber ein malignes Lymphangioendotheliom der Haut des Fuses, *Virchows Arch. f. path. Anat.* **231** 540, 1921.

entiated to justify certainty as to whether they were endothelial or whether they were metastatic cells from adenocarcinoma. The consensus of the pathologists who examined the sections was that the cells simulated most closely those seen in cases of endothelioma of the pleura, and it seemed most likely, therefore, that tumor cells from a cancer of the lung had worked into the lymphatic channels of the arm, causing obstruction and resultant elephantiasis.

The patient did not stay at the clinic for treatment. He returned home, and some high voltage roentgen therapy was administered. Five months later a physician from the patient's town wrote that he had lost about 30 pounds (13.6 Kg.) and was short of breath on exertion, although the roentgen treatment had helped to reduce the edema of the arm. It has been impossible to follow the patient further.

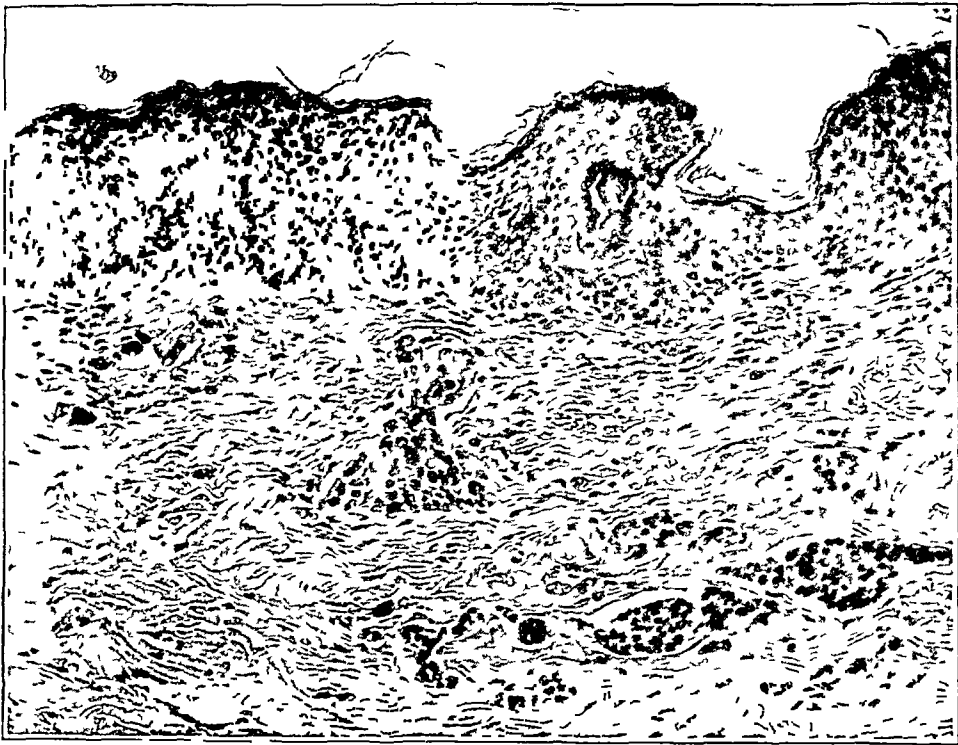


Fig 2 (case 2) —Section of a metastatic endothelioma. The lymphatic channels are packed with tumor cells,  $\times 68$ .

*Comment*—This patient's condition is an example of lymphedema and early elephantiasis of the right arm, thorax, back and flank, the result probably of direct extension of a so-called endothelioma of the pleura. The small size of the axillary nodes tended to preclude their being factors in the lymphedema of the arm and would justify the presumption that the lymphatic structures of the arm, as well as those at the level of the iliac crests and those of the right flank, were packed with tumor cells. Although vesicle-like elevations of the skin were present histopathologic studies did not permit classification of the case as an instance of one of the various forms of lymphangioma, lymphangioblastoma, endothelioma or lymphangio-endothelioma of the skin.

(Gans<sup>9</sup>) The rapid loss of weight five months after the patient had left the clinic would support the diagnosis of an internal malignant process, with metastasis to the lymphatic structures of the skin. However, in the absence of a report of postmortem examination, it can only be assumed that the diagnosis of endothelioma of the pleura, with metastasis, was correct. There was no abrasion of the skin or histologic evidence of a lesion of epitheliomatous origin.

In the literature are reports of cases of bilateral, as well as of unilateral, involvement of the extremities, the result of metastasis to the axillary and inguinal nodes from carcinoma of the internal organs. The most important point, however, is that clinically the lymphedema (mild elephantiasis) of the arm and right side of the trunk did not suggest that a malignant process was present, and that one was present was confirmed only by histopathologic study of a specimen taken for biopsy.

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9 Gans, Oscar. *Histologie der Hautkrankheiten. Die Gewebsveränderungen in der kranken Haut unter Berücksichtigung ihrer Entstehung und ihres Ablaufs*, Berlin: Julius Springer, 1928, vol. 2, p. 413.

# EVALUATION OF MEASURES OF RENAL FUNCTION IN PERSONS WITH ARTERIOSCLEROTIC BRIGHT'S DISEASE

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Although disease of the renal arterioles is the most constant morphologic expression of essential hypertension, derangement of renal function leading to death from uremia occurs in only a small number of patients with this disease. However, the attention of physicians has been so focused on the possibility of this dread outcome for persons with hypertension that they are accustomed to undertake a careful study of the renal function of their patients in the hope of assuring them that uremia is remote. It becomes pertinent to inquire into the merits of the various tests proposed for measuring renal function in the hope of selecting those which are simple and inexpensive in execution and delicate in response. The latter, more important, requirement is in part a matter of interpretation. It will depend on a strict definition of the degree of variation in result when the test is performed on normal persons. When contrasted with the result obtained in a group of persons who have a pathologic alteration of the renal parenchyma, the test giving the most consistent and pronounced variation from the norm is presumably the most delicate. This is subject to the important condition that no disturbing extraneous factor is present in either group.

We here present a study of the results given by several tests of renal function as applied to a group of 111 patients with essential hypertension. In applying the aforementioned criteria as a measure of the delicacy of the tests used, a disturbing factor of importance was encountered. It will be shown that, aside from the question of actual decrease in kidney substance, impairment of cardiac function influences the result of at least one of the tests so as to make the interpretation of correlations both difficult and obscure.

## MATERIAL AND METHODS

Hospitalized private patients were selected on the basis of a systolic blood pressure exceeding 150 mm of mercury in the absence of evidence of hemorrhagic Bright's disease or other disease accompanied by elevated blood pressure (coarctation of the aorta, hyperthyroidism, etc). There were 42 men and 69 women

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From the Laboratories of the Cottage Hospital



varying in age from 22 to 80 years, with an average of 59.1 years. None of the patients had congestive heart failure, acute infection or severe metabolic disturbances. They were fed the regular hospital diet, with no restriction of the amount of sodium chloride. Studies of renal function were not instituted until the patient had been in the hospital for several days.

The following tests were studied:

1 The excretion<sup>1</sup> of phenolsulfonphthalein was determined in 111 instances. The phenolsulfonphthalein, accurately measured in a tuberculin syringe, was given intravenously after the emptying of the bladder and the consumption of 400 cc of water. The results were reported in terms of two hour total excretion.

2 The urea clearance was studied in 33 instances. The recommended technic<sup>2</sup> was rigidly adhered to. Four hundred cubic centimeters of water was ingested at the beginning of the test in the hope of securing a maximum clearance, but frequently the rate of formation of urine did not reach 2 cc per minute. The values obtained for clearance for the first and second hour were averaged. The results were expressed in terms of the percentage of normal.<sup>3</sup>

3 The creatinine test of Major<sup>4</sup> was carried out in 34 instances, by the original technic. The results were calculated in terms of milligrams of creatinine per hundred cubic centimeters of urine.

4 The dilution and concentration test of Volhard<sup>5</sup> was also studied. The technic adopted was as follows: At 8 a. m., after the emptying of the bladder, 1,000 cc of water flavored with fruit juice was quickly consumed. Specimens of urine were collected at two hour intervals thereafter until 8 p. m., and a single specimen was collected for the twelve hour period from 8 p. m. to 8 a. m. A dry breakfast was served at 8:30 a. m., and no fluid was consumed until the evening meal. Later in the study, a dry diet was instituted for the entire twenty-four hour period following the initial ingestion of fluid. Thirst was not ordinarily complained of. The volume of urine was measured to within  $\pm 5$  cc and the specific gravity to within  $\pm 0.002$  by standardized hydrometers, with a correction for changes in temperature when indicated. Correction for albumin<sup>6</sup> was not necessary in this study.

*Choice of Normal Standards*—It is regrettable that the normal response for these tests as defined by numerous investigators has not ordinarily been expressed with a statistical statement as to normal variation. For purposes of comparison, we adopted somewhat arbitrarily the following lowest limits of normal: a phenolsulfonphthalein excretion of 55 per cent in two hours, a urea clearance of 60 per cent of normal, and a creatinine excretion in which the concentration for the second

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1 Rowntree, L. G., and Geraghty, J. T. An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonphthalein, *J Pharmacol & Exper Therap* **1** 579, 1910.

2 Moller, E., McIntosh, J. F., and Van Slyke, D. D. Studies of Urea Excretion. II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, *J Clin Investigation* **6** 427 (Dec.) 1928.

3 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry Methods, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 566.

4 Major, H. M. The Creatinine Test for Renal Function, *Arch Int Med* **33** 89 (Jan.) 1924.

5 Volhard, F., and Suter, F. Nieren und ableitende Harnwege, Berlin, Julius Springer, 1931, p. 165.

6 Lashmet, F. H., and Newburgh, L. H. The Specific Gravity of the Urine as a Test of Kidney Function, *J A M A* **94** 1883 (June 14) 1930.

hour is at least twice that of the first while that of the third hour well exceeds that of the first. The normal response to the test for dilution and concentration was given by Volhard<sup>7</sup> and others<sup>8</sup> as a swing in specific gravity from about 1.001 to 1.029 and the excretion of a volume of urine within four hours equal to the amount of fluid ingested.

TABLE 1—*Definitions of Diuretic, Diluting and Concentrating Ability and of Nocturnal Polyuria*

*Diuretic ability*

Conditions Urine formed over a four hour period of rest in bed after the ingestion of 1,000 cc of water

Odds that a normal person will secrete as small or a smaller volume than those given

Cc	Odds
648	1 in 2
448 or less	1 in 6
348 or less	1 in 12
248 or less	1 in 28
148 or less	1 in 88
48 or less	1 in 400

*Diluting ability*

Conditions Urine collected two hours after the ingestion of 1,000 cc of water

Odds that a normal person will elaborate urine having as high or a higher specific gravity than those given

Specific Gravity	Odds
1.009	1 in 2
1.012 or more	1 in 6
1.015 or more	1 in 22
1.018 or more	1 in 186
1.021 or more	1 in 2,984

*Concentrating ability*

Conditions Abstention from fluids up to 7 p. m.

Odds that a normal person will elaborate urine having as low or a lower specific gravity than those given

Specific Gravity	Odds
1.027	1 in 2
1.023 or less	1 in 8
1.019 or less	1 in 44
1.015 or less	1 in 740
1.011 or less	1 in 3,174

*Nocturnal polyuria*

Conditions Abstention from fluids for twenty four hours after the ingestion of 1,000 cc of water

Odds that a normal person will secrete as large or a larger twelve hour volume of urine than those given

Cc	Odds
236	1 in 2
406 or more	1 in 6
476 or more	1 in 44
546 or more	1 in 740
616 or more	1 in 31,746

In an attempt at simplification, our technic varied from that of Volhard. We used 1,000 cc of fluid instead of 1,500 cc as recommended by him, and we collected our specimens of urine every two hours instead of every half-hour. It became necessary to establish the limits of normal response under these modified

<sup>7</sup> Volhard and Suter,<sup>5</sup> p. 166

<sup>8</sup> Munk, Fritz. *Pathologie und Klinik der Nierenerkrankungen*, Berlin, Urban & Schwarzenberg, 1925, p. 92. Lebermann, F. *Der Wasserversuch als Nierenfunktionssprüfung*, Dresden, Theodor Steinkopff, 1932.

conditions The test was conducted on a group of 25 normal persons having a sex and age distribution similar to that of the patients with hypertension In addition, the effect of allowing or withholding breakfast on the volume and specific gravity of the urine collected over a four hour period after the ingestion of water was studied in a group of 12 nurses It was found that the volume of urine was not appreciably influenced The specific gravity of the first two hour specimens when breakfast was withheld averaged  $1.007 \pm 0.0005$  The ingestion of a dry breakfast elevated the average specific gravity to  $1.009 \pm 0.0004$  The patients in this study received breakfast during the test

Under the conditions imposed by our technic, it was found that in the four hour period undamaged kidneys excreted an average volume of urine of 648 cc, with a standard deviation of  $\pm 213$  cc The specific gravity of the first two hour specimens, regarded as a measure of diluting ability, averaged 1.009, with a standard deviation of  $\pm 0.0035$  The highest values for specific gravity encountered in specimens collected during the afternoon (concentrating ability) averaged 1.027, with a standard deviation of  $\pm 0.004$  The volume of urine excreted at night averaged 236 cc, with a standard deviation of  $\pm 70$  cc, and the specimens had an average specific gravity of 1.029, with a standard deviation of  $\pm 0.005$

Statistical definitions, under these conditions, of diuretic, diluting and concentrating ability and of nocturnal polyuria, are expressed in table 1<sup>9</sup> For purposes of comparison with the other tests, the power of dilution was considered impaired if the lowest specific gravity of a morning specimen was 1.012 or above, while the lowest limit of normal concentration for urine excreted in the afternoon was taken as 1.024

#### CORRELATION OF RESULTS

In table 2, the number of low results given by each test are tabulated and compared with each other in terms of percentage agreement Impaired diluting ability and creatinine excretion were encountered in approximately one quarter and one third, respectively, of the patients on whom these tests were made Urea clearance, concentration and phenolsulfonphthalein excretion were low in slightly less than one half of the patients in each group In general, the agreement between the results of the tests was vague and little better statistically than might have been expected as a chance occurrence, i e., a 50 per cent chance that if one test gave a low result in a person another might do likewise The only suggestive correlations were that in persons with impaired diluting ability the urea clearance was low in 66.6 per cent and that low urea clearance was accompanied by an impairment of phenolsulfonphthalein excretion in 62.5 per cent of the instances Approximately one third of each of the groups of persons having faulty diluting and concentrating abilities showed no disturbance of renal function as measured by the remaining tests A similar discrepancy of results was present in one quarter of each of the groups of patients having a low rate of phenolsulfonphthalein excretion, a low urea clearance and a low creatinine output This again conforms to the percentage of discrepancy to be expected if the results be due to chance alone

<sup>9</sup> We are indebted to Thomas Addis for this method of presentation

The urea nitrogen level of the blood was measured in 67 patients whose diluting and concentrating abilities and whose phenolsulfonphthalein excretion were studied. In 18 instances it was 20 mg per hundred cubic centimeters, or more, distributed as follows. One patient had impaired dilution, concentration and phenolsulfonphthalein excretion, 3 had lowered dilution and phenolsulfonphthalein excretion, 5 had faulty concentration and phenolsulfonphthalein excretion, while 3 had impairment of only one function—dilution, concentration or phenolsulfonphthalein excretion. An increased amount of urea nitrogen in the blood correlated more closely with a lowered phenolsulfonphthalein excretion (12 of the 18 instances) than with the results of the other tests.

Feeling that the lack of correlation between the results of these various tests might be due to our arbitrarily chosen boundaries between

TABLE 2—*Percentage Agreement Between Abnormal Results as Given by Each Test*

Test	Total Number Done	Number in Which Test Was Low	Dilution Also Low, Percentage	Concentration Also Low, Percentage	Phenol sulfon phthalein Excretion Also Low, Percentage	Urea Clearance Also Low, Percentage	Creatinine Excretion Also Low, Percentage	Reactions to All Tests Normal, Percentage
Dilution	111	28		39.3	50.0	66.6	44.4	39.3
Concentration	111	51	21.5		52.9	40.0	41.1	31.3
Phenolsulfonphthalein excretion	111	51	27.4	52.9		52.6	33.3	23.5
Urea clearance	33	16	12.5	37.5	62.5		Not done	25.0
Creatinine excretion	35	12	33.3	58.3	58.3	Not done		25.0

the normal and the abnormal, we calculated the average phenolsulfonphthalein excretion at the various levels of specific gravity encountered in the tests of dilution and concentration and at various levels of urea clearance. The results are tabulated in table 3. For purposes of better visualization, the statistical differences, derived from the standard deviations, as regards the expected occurrence of a normal phenolsulfonphthalein excretion at these levels, are expressed in terms of odds. While the average phenolsulfonphthalein excretion, as indicating a trend, was somewhat less when there was obvious impairment of renal function, as measured by the efficiency of dilution and concentration, the variation in individual responses was so great that, to judge from these data, it is hazardous to predict in a given instance whether or not a lowered phenolsulfonphthalein excretion will be accompanied by a deficiency in diluting and concentrating abilities. The same appears to be true as regards the correlation between a low urea clearance and the excretory response to phenolsulfonphthalein, but here the relatively small series of cases leaves room for doubt.

## EFFECT OF CARDIAC WEAKNESS ON MEASURES OF RENAL FUNCTION

Functional response of the kidneys is presumably extremely sensitive to changes in circulatory environment. Alteration in the amount and pressure of blood flow through the glomerular tufts or stasis in the venules, if sufficiently pronounced or prolonged, may, particularly if the amount of renal parenchyma is decreased, as it is in the arteriosclerotic kidney, detectably influence the clinical measurements of renal

TABLE 3—Average Phenolsulfonphthalein Excretion at Various Levels of Specific Gravity and of Urea Clearance

Concentration					
Specific gravity	1 015 to 1 018	1 019 to 1 022	1 023 to 1 026	1 027 to 1 030	1 031+
Average phenolsulfonphthalein excretion, percentage of normal	47.3 ± 4.6	57.9 ± 3.2	54.5 ± 2.7	57.6 ± 3.1	65.5 ± 6.9
Odds for phenolsulfonphthalein excretion, 55 per cent or over	1 in 2	1 in 2	1 in 2	1 in 2	4 in 5
Dilution					
Specific gravity	1 016 to 1 013	1 012 to 1 009	1 008 to 1 005	1 004 to 1 000	
Average phenolsulfonphthalein excretion, percentage of normal	55.2 ± 4.0	51.5 ± 3.1	58.9 ± 2.3	62.6 ± 3.7	
Odds for phenolsulfonphthalein excretion, 55 per cent or over	1 in 2	1 in 2	1 in 2	4 in 5	
Urea clearance					
Percentage of normal*	35 to 50	55 to 70	75+		
Average phenolsulfonphthalein excretion, percentage of normal	55.5 ± 3.2	44.6 ± 3.9	60.5 ± 6.6		
Odds for phenolsulfonphthalein excretion, 55 per cent or over	1 in 2	4 in 5	13 in 2		

\* Thirty four tests

function. In a hypertensive patient, particularly, with his labile circulatory apparatus, variability in blood flow might so disturb the outcome of studies of renal function as to lead to untrustworthy deductions regarding the amount of healthy renal parenchyma and to confusion in results when several measures are applied under various states of circulatory adjustment. That the rate of phenolsulfonphthalein excretion may be depressed in a patient with heart failure is attested by the observations of several workers (Frothingham and Smillie,<sup>10</sup> Hopkins and

10 Frothingham, C, Jr, and Smillie, W. G. The Relation Between the Phenolsulfonphthalein Excretion in the Urine and the Nonprotein Nitrogen Content of the Blood in Human Cases, Arch Int Med 14 541 (Oct) 1914

Jones,<sup>11</sup> Moller and Lundsgaard,<sup>12</sup> Fishberg<sup>13</sup>) Fishberg, in discussing tests of renal function in hypertension, stated "The phenol-sulfonphthalein output is more frequently subnormal (than the results of concentration tests) but this is more often the result of cardiac weakness than of impairment of renal function" MacKay,<sup>14</sup> studying the diurnal variation in urea clearance, found it most pronounced in patients with arteriosclerotic Bright's disease This he attributed to hypersensitivity of response of the vascular system to stimuli in this disease Stewart and McIntosh<sup>15</sup> studied the renal function of 38 patients with various types of compensated cardiac lesions The urea clearance was low in 8 of the 38 patients, the phenolsulfonphthalein output was low in only 1 Nineteen of 20 patients with arteriosclerotic or hypertensive heart disease had impaired renal function Of 15 patients who had previously suffered from congestive heart failure, all had a normal urea clearance and phenolsulfonphthalein excretion, but only 2 were able to concentrate and dilute well Coincident with improvement in cardiac reserve, a return of renal function toward normal was frequently observed Brems and Nielsen<sup>16</sup> have noted depression of the urea and creatinine clearance well below normal in patients with mild circulatory stasis The presence of hypertension did not appreciably influence the results

In patients with hypertension and weakness of the left ventricle, we have been struck by the frequent occurrence of a renal symptom, nocturia It often precedes by a short interval or accompanies the appearance of such symptoms as breathlessness on exertion, paroxysmal nocturnal dyspnea, anginoid pains and oppression and cough, in the absence of signs of peripheral or abdominal venous stasis It frequently disappears under a regimen of rest and digitalis This symptom

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11 Hopkins, A H, and Jones, L Studies in Renal Function, with Special Reference to Nonprotein Nitrogen and Sugar Concentration in the Blood, Phenol-sulphonphthalein Elimination and Blood Pressure, *Arch Int Med* **15**:964 (June) 1915

12 Moller, E, and Lundsgaard, C Investigations into the Value of the Phenolsulphonphthalein Test in Renal and Circulatory Diseases, *Acta med Scandinav* **63** 242, 1926

13 Fishberg, A M Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1931, p 543

14 MacKay, E M The Diurnal Variation of Urea Excretion in Normal Individuals and Patients with Bright's Disease, *J Clin Investigation* **6** 505 (Dec) 1928

15 Stewart, H J, and McIntosh, J F The Function of the Kidneys in Patients Suffering from Cardiac Disease Without Signs of Heart Failure, *J Clin Investigation* **6** 325 (Oct) 1928

16 Brems, A, and Nielsen, E Investigations on Kidney Function in Patients with Heart Ailments, *Bibliot f læger* **125** 266 (July) 1933, abstr, *J A M A* **101** 1280 (Oct 14) 1933

has received scant attention in the American literature regarding weakness of the left side of the heart, but it has been stressed on the Continent as an early and important indication of impending failure of the left ventricle (Munk, Leberman,<sup>9</sup> Volhard and Suter<sup>5</sup>) According to Volhard and Suter, it is to be distinguished from the nocturia or renal insufficiency by the fact that it is accompanied by oliguria during the day, is influenced by the fluid intake and varies with the integrity of cardiac function

Of our series of 111 patients with hypertension, 21 presented the clinical picture of weakness of the left ventricle The phenolsulfonphthalein excretion was not depressed in this group (it averaged 63 per cent, with 5 values below 55 per cent) as compared with an average of 61 per cent for the patients with good cardiac function Unfortunately, only 5 determinations of urea clearance were conducted on the patients with cardiac disease However, the urea clearance was less than 65 per cent of normal in all these patients, the highest clearance being 62 per cent and the lowest 54 per cent Of 8 tests of creatinine excretion, 4 gave abnormally low results according to our criteria These results apparently indicate that the phenolsulfonphthalein output is less influenced by cardiac weakness than is the outcome of other tests

The response to the Volhard water test by patients with weakness of the left ventricle showed statistically significant deviations both from the normal value and from the response observed in patients with hypertension having a good myocardial reserve The average volume of urine elaborated during the four hour period after the ingestion of water by the patients with cardiac weakness was  $375 \pm 41$  cc For the same period, normal persons excreted an average volume of  $648 \pm 34$  cc, and patients with noncardiac hypertensive disease, an average volume of  $525 \pm 35$  cc These results are expressed as distributions in chart 1 The lag in the excretion of water by these patients was usually compensated for by an increase in the volume of urine during the afternoon period of the test, so that under these controlled conditions their total output for the twelve-hour day and night intervals often did not vary appreciably from the normal However, this difference in the rate of formation of urine helps to explain the nocturia shown by such patients under normal conditions The delay in the diuretic response to fluids consumed during the latter part of the day necessarily results in an increase in the amount of urine passed during the night if the fluid is not to be retained in the form of edema We offer a hypothetical explanation for this phenomenon Normally the venous pressure rises in response to physical activity, but the unimpaired heart muscle responds so adequately to this burden that the rise is transitory and circulatory stasis

does not occur<sup>17</sup> If the myocardial reserve is reduced, the rise in venous pressure in response to exertion may be excessive and the period of recovery following activity may be prolonged, so that during the day some degree of venous stasis and a consequent tendency to the formation of edema may be present most of the time Ingested fluids may in part escape into the tissues as occult edema and not reach the kidneys for excretion When the patient goes to bed, the venous pressure returns to normal and remains so, and the tendency toward formation of edema is consequently dissipated Nocturnal diuresis of retained fluids might well result

We are at present studying the question of lag of excretion of water in patients with weakness of the left ventricle other than that associated with hypertension In the cases so far observed, a similar

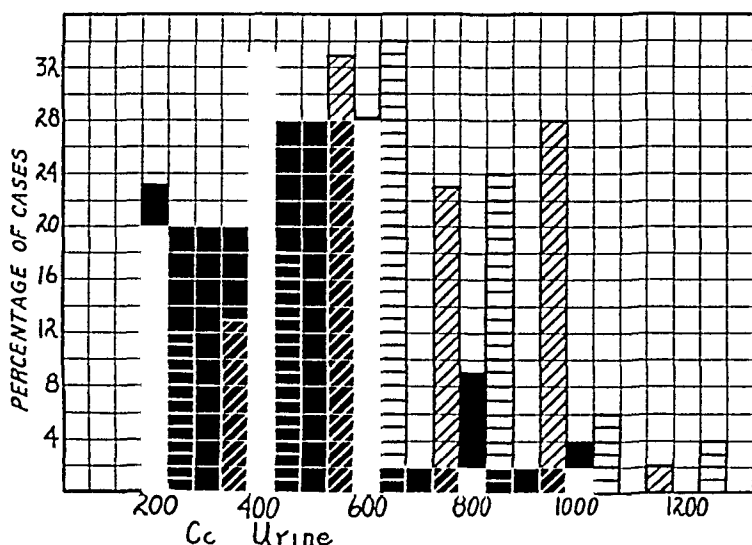


Chart 1—Distribution of the volumes of four hour specimens of urine after the ingestion of 1,000 cc of water The diagonal-shaded blocks indicate the specimens from normal subjects, the solid blocks indicate those from patients who had hypertension and weakness of the left ventricle, and the horizontal-shaded blocks indicate those from patients with hypertension and a good myocardial reserve

delay in the excretion of water is demonstrable We believe that nocturnal polyuria, when present without obvious cause in such persons, should be regarded as of cardiac origin and that it is not without diagnostic significance

In addition to impairment of diuretic response, it was found that in many of the hypertensive patients with left ventricular fatigue there was failure to elaborate urine of normally high specific gravity during the afternoon period of the Volhard test In normal persons a specific

<sup>17</sup> Eyster, J A E, and Meek, W J Studies on Venous Pressure, *Am J Physiol* **95** 294 (Nov) 1930



gravity of  $1.027 \pm 0.0008$  was reached. Hypertensive patients with a good cardiac reserve had an average specific gravity of  $1.025 \pm 0.001$ , while in those with cardiac weakness the value was lowered to an average of  $1.022 \pm 0.0014$ . Distributions are expressed in chart 2. Analysis showed that this inability to concentrate normally was independent of the slightly increased afternoon urinary volume encountered in many of these patients. Strauss<sup>18</sup> called attention to this phenomenon as an indication of beginning circulatory insufficiency. We have observed that the concentrating ability, as measured by this technic, improves coincidentally with the disappearance of cardiac symptoms. In these instances it appears that we are demonstrating by this test a disturbance of the renal circulation rather than an actual decrease in the amount of functioning parenchyma.

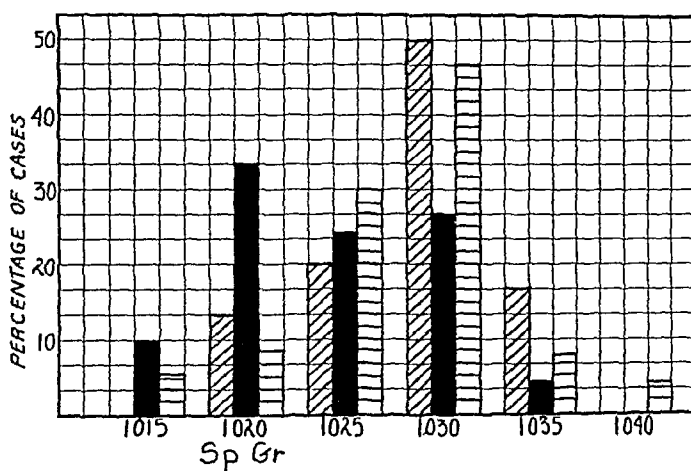


Chart 2—Distribution of the highest specific gravities of specimens collected in the afternoon period of the Volhard test. Diagonal shading indicates the specimens from normal persons, solid shading indicates the specimens from persons with hypertension and weakness of the left ventricle, and horizontal shading indicates specimens from patients with hypertension and a good myocardial reserve.

#### COMMENT

We may conclude from these studies that a judgment based on the functional examinations at our command concerning the actual amount of unscarred renal parenchyma in a patient with hypertension is a difficult undertaking. We cannot separate the kidney from a constantly changing circulatory environment, on which its functional response must in great measure depend. To produce conditions under which the response to a functional burden is measured and at the same time an unchanging renal circulation obtains is too much to hope for in

18 Strauss, H. Zur Diagnose beginnender Kreislaufinsuffizienz, *Deutsche med Wchnschr* 58:926 (June 10) 1932.

the hypertensive patient. Such factors as changing vascular tone and decreased cardiac reserve introduce variables difficult of evaluation. The more sensitive the test of function, the more may it be influenced by these factors and, therefore, the more difficult is the interpretation in terms of renal pathology. That these tests allow one to draw conclusions regarding impairment primarily of either glomerular or tubular function in persons with hypertension as some observers<sup>19</sup> have suggested, is extremely unlikely. It is, furthermore, obvious from this study that statistical conclusions regarding the incidence of faulty renal function in patients with hypertension will vary so greatly with the tests used and with the manner of their interpretation as to mean little or nothing.

As to judging the individual merits of the tests utilized in this study, we are confronted by a lack of an absolute standard for comparison of worth, and the indefinite correlation between the results of these various measurements makes the task yet more difficult. Forced to a choice we suggest that the phenolsulfonphthalein test and the water test of Volhard are to be preferred in cases of arteriosclerotic renal disease. They are economically and easily performed. They work little hardship on the patient. The phenolsulfonphthalein excretion appears to be the function least influenced by circulatory stasis, and it correlates more closely with the urea nitrogen level of the blood than do the functions measured by the other tests. The response to the water test of Volhard on the other hand may be interpreted in terms both of cardiac fatigue and of impairment of renal function. With more detailed study and refinement in technique, it may be hoped that this test will throw a clearer light on the functional interrelationship of the heart and the kidneys in persons with arteriosclerotic Bright's disease.

In answer to the question suggested at the beginning of this paper—How may one predict that a patient with hypertension will or will not die of uremia?—we agree wholeheartedly with Addis,<sup>20</sup> who said "The truth is that none of the accepted methods of clinical examination is able to differentiate with any certainty between the small number of patients who are going to die within a year or two of renal failure and the great majority who may live for decades and die of some intercurrent disease or from cardiac decompensation or cerebral thrombosis or hemorrhage."

19 Ellis, L. B. and Weiss, S. Normal Variation in Renal Function Tests with Discussion of Their Physiologic Significance, *Am J M Sc* **176** 233 (Aug.) 1933, Renal Function in Arterial Hypertension, *J A M A* **100** 875 (March 25) 1933.

20 Addis, T. The Renal Lesion in Bright's Disease, New York, Paul B. Hoeber, Inc., 1931, p. 95.

## SUMMARY

In 111 cases of arteriosclerotic Bright's disease renal function was measured by the phenolsulfonphthalein test and by the dilution and concentration test of Volhard. In addition, the urea clearance was determined in 33 patients, creatinine excretion (Major's test) in 34 and the urea nitrogen level of the blood in 67.

Standards of normal response to a slightly modified Volhard water test are given.

Impairment of diluting ability was present in one quarter of our patients with essential hypertension. The creatinine excretion was low in one third. Urea clearance, concentrating ability and phenolsulfonphthalein output were each low in one half of the patients on whom these measurements were made.

Correlation between the results of the tests was vague and little better than could be expected as a chance occurrence. In the individual instance, it was impossible in this study to predict the outcome, as regarded normality of response by our criteria, of any one test on the basis of the result given by another. A possible exception to this was that an increased amount of urea nitrogen in the blood was usually accompanied by a decreased output of phenolsulfonphthalein.

The effect of weakness of the left ventricle on the results of the tests was studied in 21 instances. The phenolsulfonphthalein output was not apparently decreased, the urea clearance was. By the Volhard technic, a lag in the excretion of water and an impairment of concentrating ability were demonstrated in these patients.

The significance of nocturia in patients with weakness of the left side of the heart, traceable to a delay in the diuretic response to fluids consumed in the latter part of the day, is discussed. A hypothetical explanation for this phenomenon is offered. When shown without obvious cause by such patients, nocturnal polyuria is primarily of cardiac origin, and its presence may be of value in the diagnosis of impending failure of the left ventricle.

It is difficult to interpret the results of tests of renal function in persons with arteriosclerotic renal disease in terms of the actual amount of healthy renal parenchyma. The value of the available tests as an aid to prognosis is disappointing.

# THE DIFFERENTIAL PLATELET COUNT

## ITS CLINICAL SIGNIFICANCE

ISADORE OLEF, M D

BOSTON

Numerous observations have been made on the total thrombocyte count in health and in disease. The differential platelet count, on the other hand, has thus far received little attention. In this investigation the behavior of the total and differential platelet counts in a number of important clinical conditions was studied and an attempt was made to analyze the results from the standpoint of their clinical significance.

Until recently the methods employed for differential platelet counting involved the use of dry stained blood films. This procedure, though simple, is inaccurate, since many of the platelets are washed off and destroyed during the process of staining, and those remaining on the glass slides or cover slips are either torn or distorted. The most accurate method for studying the morphologic characteristics of the platelets is one in which wet preparations are employed. The diluting fluid must preserve the platelets for a sufficiently long period, at least two hours, to allow an accurate total and differential count.

### METHOD

The preserving fluid employed in this investigation for both total and differential platelet counting has the following composition:

	Gm or Cc
Sodium metaphosphate	10
Sodium chloride	0.5
Dextrose	0.1
Distilled water	100.0

Under optimal conditions the platelets in this solution, when observed with the oil immersion lens, appear as free-floating, isolated, clear, highly refractile bodies with numerous spinelike processes projecting from the periphery. Most of the platelets are fairly round or ovoid, irregularly shaped thrombocytes, especially elongated forms considered by Aynaud<sup>1</sup> to be the common physiologic type, are seen rather infrequently in these

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This study was made possible by a grant from the Bingham Associates Fund. From the Medical Clinic of the Boston Dispensary, Service of Dr. Joseph H. Pratt, and the Department of Medicine, Tufts College Medical School.

<sup>1</sup> Aynaud, M. La globuline des mammifères, These de Paris, no. 93, 1909.

preparations If it is desirable to stain the platelets the following solution may be used

	Gm or Cc
Sodium metaphosphate	1 00
Sodium chloride	0 40
Dextrose	0 10
Sodium bicarbonate	0 10
Brilliant cresyl blue	0 15
Distilled water	100 0

The technic employed for the enumeration of the platelets is described by me in detail elsewhere<sup>2</sup> It may be outlined briefly as follows

The palmar surface of the finger-tip is punctured with an automatic lancet after thorough cleansing of the parts with soap and water and subsequent drying with alcohol and ether The first drop or 2 of blood is discarded A drop of the diluting fluid is then placed over the puncture wound before the blood reaches the surface of the skin, and the hand is quickly turned over so that the palmar surface is directed downward After a sufficiently large drop of blood has escaped into the drop of diluent, the mixture is applied to the surface of a small quantity (3 or 4 drops) of diluting fluid contained in a paraffin cup The mixture is gently stirred and then transferred by means of a paraffin-coated applicator to a glass slide, usually three preparations can be obtained, as the quantity of fluid in the cup yields 3 large drops A cover slip is placed over each drop, and after the preparations have been allowed to stand for from ten to fifteen minutes a relative thrombocyte-erythrocyte count is made, the oil immersion lens being used Sealing the edges of the preparations with liquid petrolatum will prevent air currents in them An erythrocyte count is then done in the usual manner, and the absolute number of platelets per cubic millimeter is determined With this method the average number of platelets per cubic millimeter in normal adults is about 500,000

The size of the platelets was estimated in a manner similar to that used in the determination of the average diameter of red cells The procedure was carried out simultaneously with the enumeration of the thrombocytes The morphologic picture of the platelets was noted in each preparation until a total of about 200 thrombocytes had been observed At first an ocular micrometer was employed, and after some experience had been gained in determining the diameter of the platelets their size was estimated by comparison with the average normal erythrocyte

#### THE DIFFERENTIAL PLATELET COUNT IN HEALTH

The average diameter of normal platelets as reported by most investigators is approximately 2.5 microns However, the platelets as observed in wet preparations vary considerably in size They can generally be divided into four distinct groups group 1, consisting of plate-

<sup>2</sup> Olef, I The Enumeration of Blood Platelets, *J Lab & Clin Med* 20 416 (Jan) 1935

lets the diameter of which is one-quarter that of a red cell, or about 1.8 microns, group 2, consisting of platelets with a diameter one-third that of a red cell, or about 2.5 microns, group 3, consisting of platelets with a diameter one-half that of a red cell or greater, or about 3.6 microns, and group 4, consisting of irregular-shaped platelets. The differential formulas for platelets of forty-five normal adults, determined by the technic just described, yielded the following averages: group 1, 18.6 per cent, group 2, 63.3 per cent, group 3, 17.4 per cent, group 4, 0.7 per cent. In 70 per cent of the counts the platelets in group 1 ranged between 10 and 30 per cent, those in group 2, between 50 and 75 per cent, and those in group 3, between 10 and 30 per cent. Approximately one-fifth of all the platelets, therefore, belong to group 1, or the small variety, most of the remaining platelets having a diameter

TABLE 1—*Differential Platelet Counts as Determined in Wet Preparations by Various Authors*

Author	Percentage Group				Preserving Fluid
	1	2	3	4	
Degkwitz Folia haemat <b>25</b> 153, 1919 1920		94.4	5.6		Sodium metaphosphate
Nygaard Proc Staff Meet, Mayo Clinic <b>9</b> 492 (Aug 15) 1934	10.0	85.0	5.0		1.6% solution of sodium oxalate
Boshamer Ztschr f d ges exper Med <b>48</b> 631, 1925 1926	17.0	74.0	4.0	5.0	14% solution of magnesium sulfate
Boshamer ibid	49.0	43.0	4.5	4.5	Tyrode's solution
Horwitz Ztschr f d ges exper Med <b>57</b> 280, 1927	49.6	30.0	19.7	0.7	Tyrode's solution
Horwitz Klin Wchnschr <b>10</b> 1613 (Aug 29) 1931	70.0	30.0		0.5 1.0	Tyrode's solution

one-third that of a red cell or greater. I have never observed giant platelets, i. e., those the size of a red cell or larger, in normal human blood, although Stahl<sup>3</sup> claims to have seen them.

Table 1 represents the differential platelet counts as determined in wet preparations by various investigators.

Apparently the differential formula obtained with Tyrode's solution yields high values of small platelets, i. e., those belonging to group 1. In fact, all investigators employing this diluent gave the average diameter of normal platelets as varying from one-eighth to one-half that of a red cell. This physiologic solution introduced by Tyrode<sup>4</sup> in 1910 is a good artificial nourishing fluid but a poor preservative of platelets. In this solution, after a relatively short time, from twenty to thirty minutes, it may be observed that the smaller platelets increase in number

3 Stahl, R. Ueber die Blutplättchen bei Infektions- und Blutkrankheiten, insbesondere über die unreifen pathologischen Plättchenformen (Thromboplasten), Ztschr f klin Med **96** 182, 1923.

4 Tyrode, M. V. The Mode of Action of Some Purgative Salts, Arch internat de pharmacol **20** 205, 1910.

as the larger forms diminish. Evidently the increase in the number of the smaller platelets is due to the rather rapid disintegration of the larger types. Many of these small platelets are microthromocytes 1 micron or even less in diameter. There has been considerable controversy as to the nature of these diminutive bodies.<sup>2</sup> From my own observations and those of many other investigators, it is highly probable that they represent either products of disintegration of platelets or other artefacts the nature of which is uncertain. The differential platelet count as obtained with this solution is therefore inaccurate. Zeller,<sup>5</sup> who employed Kemp and Calhoun's<sup>6</sup> diluting fluid, described the size of

TABLE 2—Comparative Differential Platelet Counts

Percentage Groups				Preserving Fluid	Comments
1	2	3	4		
8.3	63.6	23.9	4.2	My solution	Blood from normal adult
26.4	52.0	19.0	2.6	3.6% solution of sodium citrate	
18.8	60.0	19.4	1.9	My solution	Blood from normal adult
67.2	32.8	0	0	3.6% solution of sodium citrate	
51.3	43.4	5.3	0	0.85% solution of sodium chloride	
23.4	63.5	11.2	2.0	My solution	Blood from normal adult
60.0	35.0	5.0	0	Tyrodé's solution	
57.6	37.2	1.6	3.6	My solution, 408,000 platelets per cu mm	Amputation of foot on twentieth postoperative day (patient 46, table 10)
51.2	42.0	2.6	4.2	1.6% solution of sodium oxalate, 333,000 platelets per cu mm	
2.0	17.0	81.0	0	My solution, 224,000 platelets per cu mm	Chronic thrombocytopenic purpura (patient 29, table 7)
28.0	55.0	17.0	0	Dried blood films stained with Wright's stain, 125,000 platelets per cu mm	
4.5	39.1	54.3	2.1	My solution, 257,000 platelets per cu mm	Hemochromatosis (patient 54, table 11)
67.9	25.4	6.7	0	Dried blood films stained with Wright's stain, 340,000 platelets per cu mm	

the platelets as varying from the diameter of a red cell to the size of a pinpoint. I have never observed such marked morphologic variations of the platelets in normal blood.

Table 2 shows the simultaneous comparative observations on the same blood in the solution of sodium metaphosphate, Tyrodé's solution, isotonic solution of sodium citrate (3.6 per cent), isotonic solution of sodium oxalate (1.6 per cent) and physiologic solution of sodium chloride (0.85 per cent). Only the results obtained with the solution of sodium oxalate compare favorably with those obtained with the solution of sodium metaphosphate, although the total platelet count with the former diluent is lower. Included in this table are also the comparative

5 Zeller, H. Neue Methode der Blutplättchenzahlung nebst einigen Resultaten, *Ztschr. f. d. ges. exper. Med.* **10** 103, 1919.

6 Kemp, G. T., and Calhoun, H. Enumeration of Blood Platelets. Their Relation and That of the Leukocytes to Blood Coagulation, *Brit. M. J.* **2** 1539 (Nov. 23) 1901.

observations obtained from dry stained blood films. The blood from patients 29 and 54 presented in wet preparations considerable numbers of large and giant platelets, which were markedly reduced in the dry preparations.

### THE DIFFERENTIAL PLATELET COUNT IN DISEASE

*Anemia*—In chronic anemia, both secondary and primary, the platelet count is usually reduced, although it may be nearly normal (patient 1,

TABLE 3—*Differential Platelet Count in Anemia*

Patient	Sex	Age	Platelets per Cu mm	Differential Platelet Formula (in Percentage)				Comment	Diagnosis
				Group 1	Group 2	Group 3	Group 4		
1	F	40	450,000	24.0	44.0	30.0	2.0	1 per cent of platelets the size of a red cell	Severe secondary anemia due to bleeding hemorrhoids
2	M	42	281,000	8.3	45.9	44.9	0.9	Numerous large platelets, many giant platelets	Primary hypochromic anemia, bleeding hemorrhoids
3	M	33	250,000	29.2	39.8	27.7	3.3		Chronic bleeding peptic ulcer, red cell count, 2,290,000
			468,000	36.4	50.0	12.5	1.1		1 month later, red cell count, 5,420,000
4	M	19	437,000	15.0	73.5	10.6	0.9		Normal
			372,000	49.0	45.0	4.0	2.0		20 hours after removal of 500 cc. of blood for transfusion
			677,000	66.0	30.5	3.5			5 days later
5	M	56	293,000	14.7	55.4	27.4	2.5		Primary hypochromic anemia
			451,000	22.7	56.4	20.0	0.9		After 1 month with iron treatment
6	F	41	547,000	22.0	66.0	12.0			Primary hypochromic anemia under iron treatment
7	F	42	382,000	8.1	63.8	22.5	5.6		Primary hypochromic anemia
8	M	68	149,000	53.3	37.5	5.4	1.8		Pernicious anemia, red cell count, 2,200,000
			508,000	32.2	47.1	20.7			After 9 months' treatment with liver extract, red cell count, 5,050,000
9	M	37	421,000	19.4	62.5	18.1			Pernicious anemia under liver treatment
10	F	40	512,000	10.0	55.0	5.0			Pernicious anemia under liver treatment

table 3) The differential formula may be either normal or abnormal. The deviation from the normal in the differential platelet count is usually due to the presence of increased numbers of small platelets, i.e., those belonging to group 1. As the total count rises the number of small platelets increases until the normal level is reached, when the differential formula also gradually reverts to normal. The total thrombocyte and differential counts, therefore, are normal if the anemia has been under adequate treatment (with iron or liver) for a sufficiently long period (patients 3, 5, 6, 8, 9, 10). Patients 1 and 2 exhibited



abnormal bone marrow reactions as judged by the presence of giant platelets in the peripheral blood Hayem<sup>7</sup> and Nattan-Larrier<sup>8</sup> also observed giant platelets in chronic anemias

In the anemias due to acute loss of blood there is usually an increase in platelets following an initial drop The differential formula is abnormal, owing to the presence of many small forms This is illustrated by chart 1, for patient 4, who acted as a donor for a blood transfusion Degkwitz,<sup>9</sup> however, noted giant platelets in this condition Thrombocytosis following acute loss of blood has been observed by Mackay,<sup>10</sup> Richardson<sup>11</sup> and Clough,<sup>12</sup> and is, according to Hartung,<sup>13</sup> a factor of

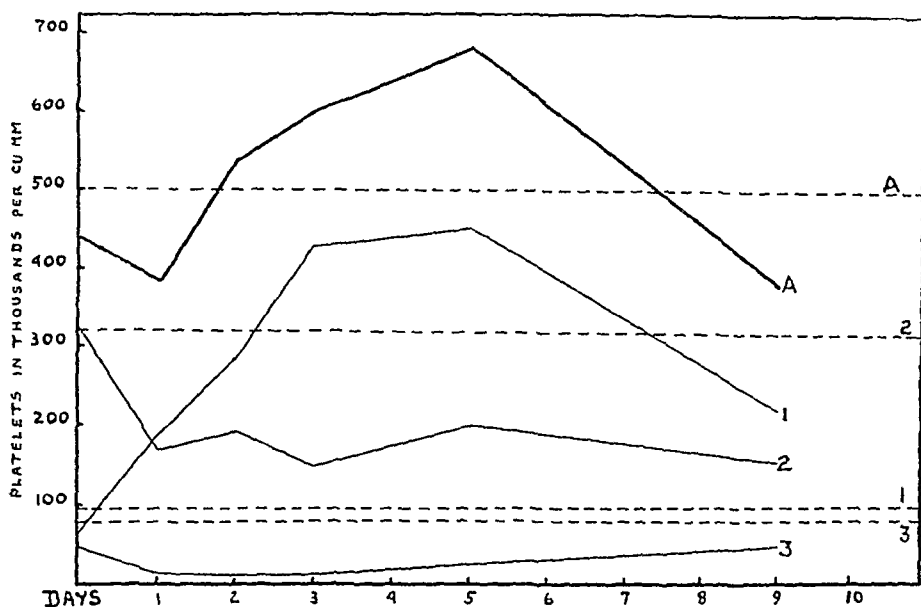


Chart 1 (patient 4) —Behavior of platelets following acute loss of blood In all the charts the dotted line *A* represents the normal platelet level, and the dotted lines 1, 2 and 3, the normal absolute levels of the corresponding groups The continuous line *A* represents the behavior of the total platelet count, and the continuous lines 1, 2 and 3, that of the absolute counts of the corresponding groups

7 Hayem, G. *Leçons sur les maladies du sang*, Paris, G. Masson, 1900

8 Nattan-Larrier, L. *Sur quelques caracteres morphologiques des hémoblastes*, *Compt rend Soc de biol* **63** 771 (Dec 28) 1907

9 Degkwitz, R. *Studien über Blutplättchen*, *Folia haemat* **25** 153, 1919-1920

10 Mackay, W. *The Blood Platelet Its Clinical Significance*, *Quart J Med* **24** 285 (April) 1931

11 Richardson, F. L. *Effect of Severe Hemorrhage on the Number of Blood Plates in Blood from the Peripheral Circulation of Rabbits*, *J M Research* **8** 99, 1904-1905

12 Clough, P. W. *Diseases of the Blood*, New York, Harper & Brothers, 1929

13 Hartung, D. *Zur Verhütung der Thrombose und Embolie*, *Deutsche Ztschr f Chir* **229** 271, 1930

some importance in the predisposition to the development of spontaneous thrombosis as seen postoperatively and in patients with polycythaemia vera treated with phenylhydrazine and venesection or with venesection alone

*Polycythaemia Vera*—Thrombocytosis is frequently encountered in this condition (table 4), the total platelet count, however, may be normal or reduced. The abnormality in the differential formula is due either to a shift to the left, owing to the appearance of increased numbers of small platelets (patients 11, 12 and 15), or to a shift to the right, owing to the presence of large and giant platelets (patient 14). Barta<sup>14</sup> observed giant platelets in the dry stained blood smears obtained from patients with this condition, and Minot<sup>15</sup> noted megakaryocytes in these smears.

TABLE 4—*Differential Platelet Count in Polycythaemia Vera*

Patient	Sex	Age	Platelets per Cu Mm	Differential Platelet Formula (In Percentage)				Comment	Treatment
				Group 1	Group 2	Group 3	Group 4		
11	F	33	637,000	48.0	45.0	7.0			
12	M	37	292,000	45.0	48.0	7.0			
13	F	70	581,000	25.8	41.0	33.2			
14	M	60	462,000	25.0	40.0	35.0		Many large platelets	Phenylhydrazine
15	F	50	900,000	42.6	41.7	6.1	9.6		Phenylhydrazine

The total and differential platelet counts at times assume considerable importance by affording criteria as to the type of treatment to be employed in this disease. Patients with polycythaemia vera occasionally exhibit a tendency to the development of spontaneous thrombosis, especially after treatment with phenylhydrazine and venesection. It is well known that phenylhydrazine, when administered to these patients, frequently causes an increase in the number of platelets, often to a high level. That phenylhydrazine may cause extreme thrombocytosis by irritating the giant cells of bone marrow is evident from the observations of Frey,<sup>16</sup> who noted that the highest number of megakaryocytes occurred in the bone marrow of a patient with polycythaemia vera (6,457 megakaryocytes per cubic millimeter in the marrow of the femur instead of

14 Barta, I. Beitrag zur Entstehung der Thrombose bei Polyzythämie nach Phenylhydrazinbehandlung, *Deutsches Arch. f. klin. Med.* **162** 185, 1928.

15 Minot, G. R. Megakaryocytes in the Peripheral Circulation, *J. Exper. Med.* **36** 1 (July) 1922.

16 Frey, H. C. Das Verhalten der Megakaryozyten im menschlichen Knochenmark und deren Beziehungen zum Gesamtorganismus, *Frankfurt Ztschr. f. Path.* **36** 419, 1928.

from 200 to 250 megakaryocytes found normally) The observations of Gaspar<sup>17</sup> agree with those of Frey In fact, the highest platelet count in man reported in the literature occurred in a patient with polycythemia who was treated with phenylhydrazine, in whom the count rose to 3,100,000 per cubic millimeter (Jurgens and Bach<sup>18</sup>) The phenylhydrazine thrombocytosis is frequently associated with the presence of numerous small platelets, which have been observed by Barta,<sup>14</sup> Zeller,<sup>19</sup> Jurgens and Naumann<sup>20</sup> and Jurgens<sup>21</sup> to agglutinate readily These two factors, extreme thrombocytosis and increased agglutinability of the platelets, create conditions favoring the development of spontaneous thrombosis in these patients A similar reaction is noted after venesection, as has been emphasized by Hartung<sup>13</sup> Therefore, the suggestion of Falconer<sup>22</sup> that polycythemia be treated with phenylhydrazine and venesection may be a rather dangerous therapeutic procedure in patients whose platelet count is considerably elevated For patients exhibiting marked thrombocytosis associated with the presence of large numbers of small platelets the safest form of treatment is roentgen irradiation

*Leukemia*—In chronic lymphatic leukemia (table 5) the total thrombocyte count is usually reduced However, it may be normal (patient 19) Thrombopenia is the rule in the aleukemic leukoses In chronic myelogenous leukemia the total platelet count is usually elevated, often to a moderately high level Stahl,<sup>3</sup> however, observed relatively slight increases in the number of platelets in myelogenous leukemia His results can be ascribed to the employment of Fonio's<sup>23</sup> inaccurate method for the enumeration of platelets

The deviation from the normal in the differential platelet count in leukemia is usually due to the presence of many small platelets In myelogenous leukemia, in addition, large and giant platelets are fre-

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17 Gaspar, S Untersuchungen über Ursprung, Zahl und Form der Blutplättchen und über das Benehmen der Knochenmarkriesenzellen (Megakaryozyten) unter normalen und pathologischen Verhältnissen, Frankfurt Ztschr f Path **34** 460, 1926

18 Jurgens, R, and Bach, K Thrombosebereitschaft bei Polycythaemia Vera, Deutsches Arch f klin Med **176** 726 (Aug) 1934

19 Zeller, H Die Differenzierung der Blutplättchen, Deutsche med Wchnschr **47** 505 (May 5) 1921

20 Jurgens, R, and Naumann, W Klinische und experimentelle Untersuchungen über Funktionen der Blutplättchen, Deutsches Arch f klin Med **172** 248 (Dec) 1931

21 Jurgens, R Beitrag zur Pathologie und Klinik der Blutungsbereitschaft, Ztschr f klin Med **123** 649, 1933

22 Falconer, E H Treatment of Polycythemia The Reticulocyte Response to Venesection, Phenylhydrazin and Radiation, Ann Int Med **7** 172 (Aug) 1933

23 Fonio, A Ueber ein neues Verfahren der Blutplättchenzahlung, Deutsche Ztschr f Chir **117** 176 (June) 1912

quently found (patients 17 and 18) Abnormally large platelets in myelogenous leukemia have also been noted by Degkwitz,<sup>9</sup> Hayem<sup>7</sup> and Puchberger.<sup>24</sup> Minot<sup>15</sup> and Minot and Buckman,<sup>25</sup> moreover, observed various-sized megakaryocytes in dry stained blood smears obtained from patients with this condition

*Malignant Growths*—In patients with a malignant growth (table 6) the total platelet count is frequently elevated, however, it may also be normal or reduced. Marked thrombopenia, on the other hand, is rare and usually indicates invasion of bone marrow by the malignant process. The abnormality in the differential formula is due either to an increase in the number of small forms or to the presence of large and giant platelets.

TABLE 5—*Differential Platelet Count in Leukemia*

Patient	Sex	Age	Platelets per Cu Mm	Differential Platelet Formula (in Percentage)				Comment	Diagnosis
				Group 1	Group 2	Group 3	Group 4		
16	M	46	736,000	37.8	45.4	5.0	10.9		Chronic myelogenous leukemia
			518,000	45.8	46.4	7.8			After roentgen treatment
17	F	56	1,319,000	40.0	40.0	18.0	2.0	Many large platelets	Chronic myelogenous leukemia
18	F	42	252,000	32.8	50.4	10.8		Occasional giant platelets	Aleukemic myelogenous leukemia
19	M	28	465,000	9.0	61.5	24.0	2.5		Chronic lymphatic leukemia
20	F	60	179,000	63.0	24.0	2.0			Aleukemic lymphatic leukemia

In a patient with Hodgkin's disease (patient 28) the thrombocytosis present was associated with a fairly normal differential formula. Following treatment with roentgen irradiation there was a drop in the total count, and then a rise above the initial level, with the simultaneous appearance of large numbers of small platelets. Thrombocytosis in Hodgkin's disease has been noted also by Minot,<sup>15</sup> Bunting<sup>26</sup> and Crawford,<sup>27</sup> the former two investigators, in addition, have observed many giant platelets and megakaryocytes in dry stained blood films.

24 Puchberger, G. Bemerkungen zur vitalen Färbung der Blutplättchen des Menschen mit Brillantkresylblau, Virchows Arch f path Anat **171** 181, 1903

25 Minot, G. R., and Buckman, T. E. The Blood Platelets in the Leukemias, Am J M Sc **169** 477 (April) 1925

26 Bunting, C. H. Blood Platelets and Megalokaryocytes in Hodgkin's Disease, Bull Johns Hopkins Hosp **22** 114 (April) 1911

27 Crawford, G. J. Blood Platelets in Anemias and Acute Infections. Their Number and Morphology, Lancet **2** 595 (Sept 20) 1924

The occurrence of thrombocytosis in patients with a malignant growth was first noted by Hayem<sup>7</sup> and is in accord with the observations of Frey<sup>16</sup> and Gaspari,<sup>17</sup> who found increased numbers of megakaryocytes in the bone marrow of these patients. The original observations of Hayem have been amply confirmed by many subsequent investigators. According to Morrison,<sup>28</sup> thrombocytosis is by far the most outstanding hematologic finding in cases of a malignant growth. The tendency to nonmalignant thrombosis in these cases was ascribed by Naegeli<sup>29</sup> to this factor. Noeff<sup>30</sup> expressed the opinion that thrombocytosis is found only in patients with bleeding neoplasms. Perl,<sup>31</sup> on the other hand, employing Fonio's method for the enumeration of platelets, found nor-

TABLE 6—*Differential Platelet Count in Cases of a Malignant Growth*

Patient	Sex	Age	Platelets per Cu Mm	Differential Platelet Formula (in Percentage)				Comment	Diagnosis
				Group 1	Group 2	Group 3	Group 4		
21	M	60	391,000	10.0	35.0	55.0		Many large and giant platelets	Cancer of colon
22	M	60	375,000	27.0	64.5	8.5			Cancer of stomach
23	M	57	721,000	16.0	49.0	35.0			Cancer of stomach
24	F	52	1,023,000	68.7	26.5	3.1	1.7	Many large platelets, occasional giant platelets	Cancer of stomach
25	F	50	385,000	12.0	40.0	48.0			Cancer of neck
26	F	59	601,000	56.0	36.8	5.6	1.6	Occasional giant platelets	Cancer of breast
27	M	60	607,000	12.4	61.4	24.8	1.4		Cancer of lung
28	M	38	469,000	45.1	45.9	9.0			After roentgen treatment
			677,000	23.6	54.8	21.6			Hodgkin's disease
			627,000	35.5	47.8	16.7			After roentgen treatment
			702,000	62.1	29.3	2.3	6.3		2 months later

mal platelet counts in twenty-seven of thirty-three patients with a malignant growth, the remaining six exhibiting definite thrombopenia, thrombocytosis was not observed in a single instance. Marked thrombopenia is rare. Cohen<sup>32</sup> in 1929 reported a case and cited eight others

28 Morrison, M. An Analysis of the Blood Picture in One Hundred Cases of Malignancy, *J. Lab. & Clin. Med.* **17** 1071 (Aug.) 1932.

29 Naegeli, O. *Blutkrankheiten und Blutdiagnostik*, ed. 5, Berlin, Julius Springer, 1931.

30 Noeff, K. Neuere über die Methodik der Thrombozytenzählung und ihre praktische Verwendung insbesondere bei der Diagnose des Karzinoms, *Wien. klin. Wchnschr.* **48** 235 (Feb. 22) 1935.

31 Perl, C. Die Thrombocyten beim Carcinom, *Ztschr. f. klin. Med.* **122** 253, 1932.

32 Cohen, J. Het bloedbeeld bij metastatisch beenmergcarcinoom, *Nederl. tijdschr. v. geneesk.* **73** 5485 (Nov. 23) 1929.

from the literature. Similar cases have been reported by Rawitsch and Warschawskaja<sup>33</sup> and Beiglbock.<sup>34</sup> In fact, Beiglbock stated that in elderly patients unexplained purpura associated with thrombopenia may be the first sign of an occult cancer with metastases to bone marrow.

Abnormalities in the differential formula associated with the presence of large and giant platelets have been observed also by Rosenbaum<sup>35</sup> and Pelczar and Koloszynski.<sup>36</sup> The former investigator, moreover, expressed the opinion that the appearance of abnormally large platelets is even more characteristic than the thrombocytosis, the presence of these macrothrombocytes often being of diagnostic significance in cases in which a malignant growth is suspected.

*Essential Thrombocytopenic Purpura*—The blood platelet has been described as the "guide in the labyrinth of purpuric diseases." Ever since Brohm's<sup>37</sup> discovery of the reduction in the number of platelets in chronic thrombocytopenic purpura, thrombopenia has been regarded as one of the most characteristic features of this disease. Normal or only slightly reduced platelet counts in cases of purpura haemorrhagica have been reported by Jones and Tocantins<sup>38</sup>. These cases, however, were probably instances of fibrinopenia of Rabe and Salomon,<sup>39</sup> of "purpura dysovarica" of Nagy<sup>40</sup> or of hereditary hemorrhagic thrombasthenia, which was described first by Glanzmann<sup>41</sup> and more recently by Jurgens.<sup>42</sup>

Frequently the platelets observed are too few in number for accurate differentiation. In general, however, the abnormality in the differential

33 Rawitsch, M. S., and Warschawskaja, B. B. Zum hamatologischen Bilde der metastatischen Geschwulste. *Folia haemat.* **44** 150, 1931.

34 Beiglbock, W. Ueber die Bedeutung hamorrhagischer Diathesen bei occulten Carcinomen, *Ztschr. f. klin. Med.* **124** 411, 1933.

35 Rosenbaum, B. N. Zur Frage der Blutplättchen bei malignen Tumoren. *Zentralbl. f. Chir.* **51** 305 (Feb. 23) 1924.

36 Pelczar, K., and Koloszynski, E. Les thrombocytes dans le cancer experimental, *Verhandl. internat. Kong. vergl. Path.* **2** 514, 1931, abstr., *Kongresszentralbl. f. d. ges. inn. Med.* **68** 817, 1933.

37 Brohm, cited by Pratt, J. H. Purpura and Hemophilia, in Osler, W., and McCrae, R. *Modern Medicine*, ed. 3, Philadelphia, Lea & Febiger, 1927.

38 Jones, H. W., and Tocantins, L. M. A Discussion of the Classification and Etiology of Purpura Hemorrhagica, *M. Clin. North America* **16** 181, 1932; The Treatment of Purpura Hemorrhagica, *J. A. M. A.* **100** 83 (Jan. 14) 1933.

39 Rabe, F., and Salomon, E. Ueber Faserstoffmangel im Blute bei einem Falle von Hamophilie, *Deutsches Arch. f. klin. Med.* **132** 240 (May) 1920.

40 Nagy, G. Ist es berechtigt, im Rahmen der hamorrhagischen Diathesen eine "Purpura Dysovarica" als selbständiges Krankheitsbild anzunehmen? *Ztschr. f. klin. Med.* **102** 284, 1925.

41 Glanzmann, E. Hereditäre hamorrhagische Thromboasthenie. Ein Beitrag zur Pathologie der Blutplättchen, *Jahrb. f. Kinderh.* **88** 1 and 113, 1918.

42 Jurgens, R. Ueber erbliche Thrombopathien, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* **46** 104, 1934.

count is due either to the presence of many large and giant platelets or to a relative increase in the smaller forms (table 7) Hess<sup>43</sup> likewise stated that in purpura the morphologic picture of the platelets is abnormal, owing to the presence of macrothrombocytes and microthrombocytes. This is at variance with the observations of Nygaard<sup>44</sup> that in purpura from 40 to 90 per cent of the platelets belong to his group 1, or the small variety (about 1.5 microns in diameter). There was usually a tendency for the differential formula to remain abnormal in one direction, either by a shift to the right toward the larger forms or by a shift to the left toward the smaller types, even after the total platelet count had risen to a considerably high level. Thus, in patient 29, 1.5 per cent of all the platelets were in group 1 when the count was 127,000 per

TABLE 7—*Differential Platelet Count in Chronic Thrombocytopenic Purpura*

Patient	Sex	Age	Platelets per Cu Mm	Differential Platelet Formula (in Percentage)				Comment	Treatment
				Group 1	Group 2	Group 3	Group 4		
29	M	25	127,000	1.0	15.0	84.0		Numerous giant platelets	2 months later, after having received 3 blood transfusions
			424,000	5.0	20.0	75.0		Numerous giant platelets	
30	F	27	70,000	33.3	61.3	5.4		Occasional giant platelets	After 2 months' treatment with a high protein and high fat diet 4 months later
			314,000	40.0	46.0	6.0	8.0		
			370,000	33.0	36.0	28.0	3.0		
31	F	31	62,000	20.0	50.0	30.0			

cubic millimeter, and 5 per cent of the platelets were in the same group after the count had increased to 424,000. Likewise, in patient 30 there was a considerable proportion of small thrombocytes (33 per cent) when the total count was 70,000 per cubic millimeter and a similar proportion of platelets in the same group after the count had risen to 370,000.

There seems to be a relation between the morphologic picture of the platelets and the function that they exhibit. Platelets of normal morphologic characteristics may or may not possess abnormal function, platelets of abnormal morphologic characteristics, however, always pos-

43 Hess, A. F. The Blood and Blood Vessels in Hemophilia and Other Hemorrhagic Diseases, *Arch. Int. Med.* **17**: 203 (Feb.) 1916.

44 Nygaard, K. K. A Direct Method of Counting Platelets in Oxalated Plasma, *Proc. Staff Meet., Mayo Clin.* **8**: 365 (June 14) 1933. Coagulability of the Blood Plasma and Changes in the Number of Platelets in Thrombocytopenic Purpura, *ibid.* **9**: 492 (Aug. 15) 1934.

sess abnormal function. The large types of platelets are giants morphologically and dwarfs functionally. Thus, Juigens and Naumann<sup>20</sup> noted in a case of essential thrombopenia many giant platelets which agglutinated poorly until after splenectomy, when many small platelets appeared, with the simultaneous shortening of the agglutination time. In patient 29 bleeding from the gastro-intestinal tract occurred whenever the platelet count dropped to 200,000 per cubic millimeter, the differential formula presented numerous large and giant, apparently poorly functioning platelets. Duke's<sup>45</sup> critical thrombocyte levels for hemorrhagic tendencies and Opitz and Schober's<sup>46</sup> critical platelet levels for clot retraction lose their relative significance when considered from this aspect, since they fail to correlate the quantitative aspects and the functional properties of the platelets.

*Jaundice*—In patients with jaundice (table 8) the total platelet count is frequently reduced. The differential formula is abnormal,

TABLE 8—*Differential Platelet Count in Jaundice*

Patient	Sex	Age	Plate lets per Cu Mm	Differential Platelet Formula (in Percentage)				Diagnosis
				Group 1	Group 2	Group 3	Group 4	
32	F	35	255,000 437,000	36.6 12.7	37.8 68.6	24.4 18.7	.2	Catarrhal jaundice 2 months later, patient well
33	M	30	306,000 485,000	37.0 24.0	51.0 60.0	8.0 16.0	1.0	Catarrhal jaundice 1 month later, patient well
34	M	31	402,000	61.8	35.2	3.0		Catarrhal jaundice
35	M	23	406,000	31.0	41.0	28.0		Chronic hemolytic jaundice
36	F	28	265,000	34.3	50.0	11.7		Jaundice due to arsphenamine hepatitis
37	F	74	187,000	59.5	34.9	5.6		Obstructive jaundice

owing to the presence of increased numbers of small platelets. Decrease in the number of thrombocytes in jaundice has been observed also by Horwitz,<sup>47</sup> Blum<sup>48</sup> and Storz and Schlunbaum.<sup>49</sup> Jones and Minot,<sup>50</sup> however, noted in dry stained blood films from jaundiced patients that the number of platelets was normal up to the time that improvement

45 Duke, W. W. The Behavior of the Blood Platelets in Toxemias and Hemorrhagic Diseases. A Preliminary Report, *Bull. Johns Hopkins Hosp.* **23** 144 (May) 1912.

46 Opitz, H., and Schober, W. Klinische und experimentelle Studien über die Bedeutung der Blutplättchen für die Retraktivität des Blutkuchens, *Jahrb. f. Kinderh.* **103** 189, 1923.

47 Horwitz, S. Die klinische Bedeutung der Blutplättchenzahlmethode nach Hofmann-Flossner, *Ztschr. f. d. ges. exper. Med.* **57** 380, 1927.

48 Blum, M. K. Ueber Blutkörpercheneinschlüsse bei Ikterus gravis, *Med. Klin.* **20** 1577 (Nov. 9) 1924.

49 Storz, H., and Schlunbaum, H. Ein klinischer Beitrag zur Pathologie der Blutgerinnung, *Klin. Wchnschr.* **12** 184 (Feb. 4) 1933.

50 Jones, C. M., and Minot, G. R. Infectious (Catarrhal) Jaundice. An Attempt to Establish a Clinical Entity, *Boston M. & S. J.* **189** 531 (Oct. 18) 1923.



began, when an increase occurred, with the simultaneous appearance of many small and large platelets

Several theories have been advanced to explain the susceptibility of jaundiced patients to bleeding, such as fibrinopenia (Whipple and Hurwitz<sup>51</sup>), a low serum calcium content (Buchbinder and Keim<sup>52</sup>), a decrease in the amount of diffusible calcium (Emerson<sup>53</sup>) and the accumulation in the blood of excessive amounts of cysteine and related forms of mercaptan (Cair and Foote<sup>54</sup>). The platelets, however, are intimately related to the coagulation of the blood and the syneresis of blood clots. It is probable that the deviation from the normal in their number and morphologic picture constitutes another contributory factor in the pathogenesis of the tendencies to bleeding exhibited by these patients.

*Infection*—During acute infectious diseases the platelets behave in a characteristic manner, as illustrated in the case of patient 38 (table 9

TABLE 9—*Differential Platelet Count in Infection*

Patient	Sex	Age	Plate lets per Cu Mm	Differential Platelet Formula (in Percentage)				Diagnosis
				Group 1	Group 2	Group 3	Group 4	
38	M	46	320,000	10.0	60.7	29.3		Acute stage of lobar pneumonia
			1,344,000	52.5	37.9	5.1	4.5	Two days after crisis
39	M	15	790,000	48.5	42.7	6.2	2.6	Patient convalescing from lobar pneumonia
40	M	55	611,000	62.5	31.0	1.9	4.6	Bronchiectasis (low grade sepsis)
41	F	30	586,000	17.2	61.4	21.4		Pulmonary tuberculosis (slightly active)
42	F	40	658,000	57.8	37.1	3.1	3.1	Pulmonary tuberculosis (moderately active)
43	M	21	204,000	50.0	40.0	6.0	4.0	Subacute bacterial endocarditis

and chart 2). In the acute stage of the illness there is thrombopenia, followed during convalescence by thrombocytosis, which may be considerable. The differential formula is characterized by a shift to the left, owing to the appearance of numerous small platelets. I have not observed giant platelets in infectious diseases, although Degkwitz<sup>9</sup> and Minot<sup>15</sup> claim to have seen them in dry stained blood smears.

In chronic infections the total thrombocyte count may be elevated or reduced. The differential formula is abnormal, owing to the presence

51 Whipple, G. H., and Hurwitz, S. H. Fibrinogen of the Blood as Influenced by the Liver Necrosis of Chloroform Poisoning, *J. Exper. Med.* **13** 136 (Jan.) 1911.

52 Buchbinder, W. C., and Kern, R. Blood Calcium Deficiency in Experimental Obstructive Jaundice, *Am. J. Physiol.* **80** 273 (May) 1927.

53 Emerson, W. C. The Distribution of Calcium of Jaundiced and Alcoholic Dogs, *J. Lab. & Clin. Med.* **14** 122 (Nov.) 1928.

54 Carr, J. L., and Foote, F. S. Progressive Obstructive Jaundice. Changes in Certain Elements of the Blood and Their Relation to Coagulation, *Arch. Surg.* **29** 277 (Aug.) 1934.

of increased numbers of small platelets. Tuberculosis presents a notable exception, for in this disease the platelets are nearly always increased in number. More significant than the thrombocytosis, however, is the differential platelet count, which in active cases exhibits a shift to the left. The thrombocytosis in tuberculosis has been observed by many early investigators, Halla<sup>55</sup> Afanassiew<sup>56</sup> and van Emden<sup>57</sup> among

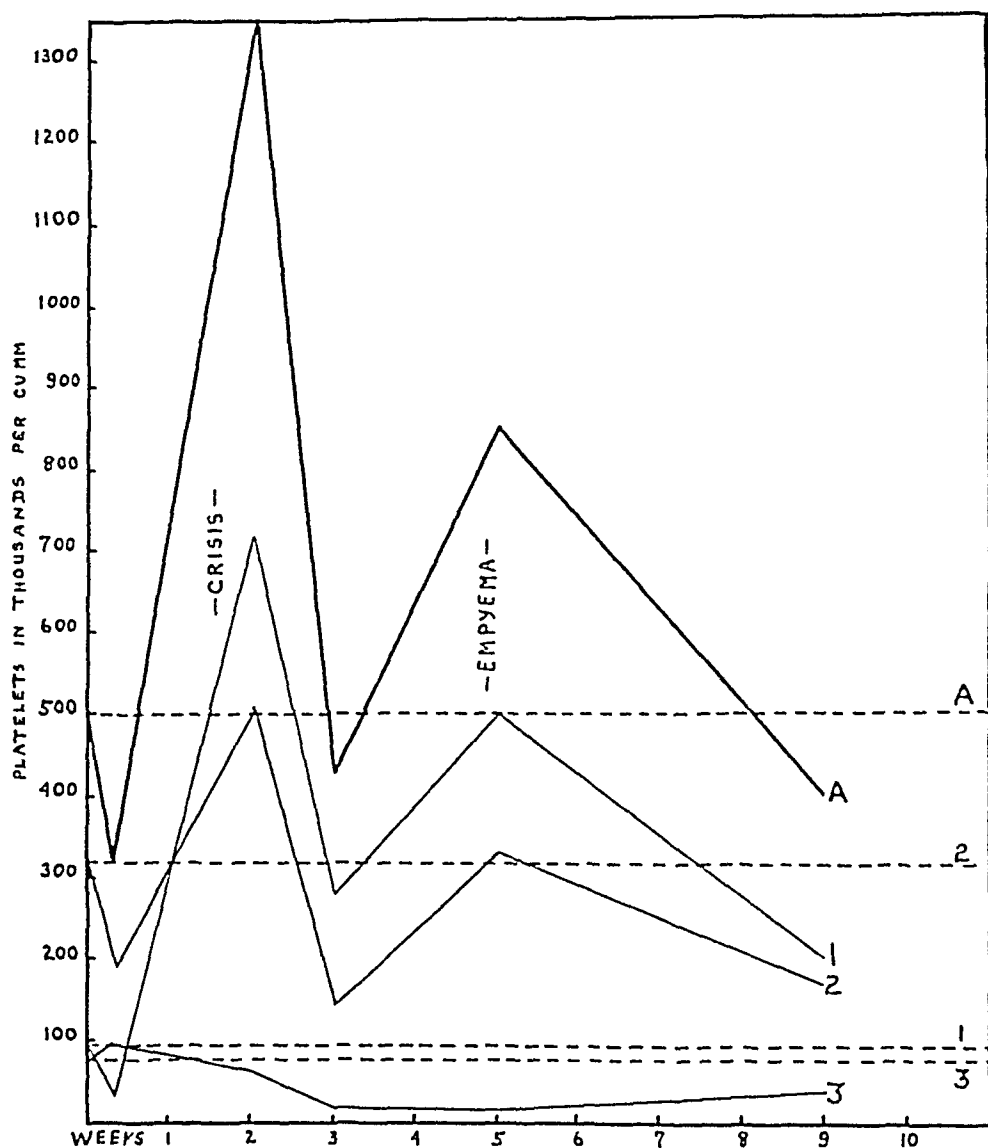


Chart 2 (patient 38) —Behavior of platelets during the course of lobar pneumonia complicated by empyema

<sup>55</sup> Halla, A. Ueber den Haemoglobingehalt des Blutes und die quantitativen Verhältnisse der roten und weissen Blutkörperchen bei akuten fieberhaften Krankheiten, *Ztschr f Heilk* **4** 331, 1883

<sup>56</sup> Afanassiew, M. Ueber den dritten Formbestandtheil des Blutes im normalen und pathologischen Zustande und über die Beziehung desselben zur Regeneration des Blutes, *Deutsches Arch f klin Med* **35** 217 (Aug) 1884

<sup>57</sup> van Emden, J. E. G. Klinische Untersuchungen über die Blutplättchen, *Fortschr d Med* **16** 241, 1898

others Bannerman,<sup>58</sup> Brock and Rake<sup>59</sup> and Brock<sup>60</sup> stated that the thrombocytosis is associated with activity of the tuberculous lesion and that a return to normal figures indicates a subsidence of the activity of the process, in other words, an inverse relationship appears to exist between thrombocytosis and the subject's resistance to the disease

Hayem<sup>61</sup> and his pupil Reyne were first to observe the decrease in the number of platelets (*crise hématoblastique*) at the onset of acute infections According to Hatzky,<sup>62</sup> this initial thrombopenia may be sufficiently severe that hemorrhagic manifestations may appear In rheumatic fever high values for platelets have been noted at the onset (Mackay,<sup>10</sup> Naegeli<sup>29</sup> and Doenecke<sup>63</sup>) The platelets behave similarly in the exanthems (Glanzmann<sup>41</sup>) There is thrombocytosis during the incubation period of acute infectious diseases in children (Beck<sup>64</sup>)

The thrombopenia at the onset of acute infections is attributed to the clumping of the platelets with the micro-organisms introduced into the circulation This phenomenon was first described by Levaditi<sup>65</sup> in 1901 and was interpreted by Delrez and Govaerts<sup>66</sup> and by Govaerts<sup>67</sup> as indicating that the platelets, like the leukocytes, attach themselves to foreign bodies such as bacteria, causing their destruction and removal from the circulation, if the organism introduced into the circulation is of such virulence that no agglutination with the platelets occurs, septicemia follows The phenomenon of agglutination, therefore, is evidence of the rôle that the platelets play in aiding the body in combating infection

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58 Bannerman, R G Blood-Plate Counts in Pulmonary Tuberculosis, *Lancet* **2** 593 (Sept 20) 1924

59 Brock, R C, and Rake, G W Some Observations on Blood-Platelets, *Guy's Hosp Rep* **9** 451 (Oct) 1929

60 Brock, R C Observations on the Platelet Count in Tuberculosis, *Tubercle* **15** 241 (March) 1934

61 Hayem, G Recherches sur l'évolution des hématies dans le sang de l'homme et des vertebres, *Arch de physiol norm et path* **5** 692, 1878

62 Hatzky, K Zur Frage der akuten Thrombopenien, *Folia haemat* **47** 375, 1932

63 Doenecke, F Ueber die Veränderungen der Blutplättchenzahlen bei akuter diffuser Glomerulonephritis und ihre Bedeutung für die Pathogenese, *Ztschr f klin Med* **121** 121, 1932

64 Beck, D Ueber das Verhalten der Blutplättchen bei Infektionen, *Monatsschr f Kinderh* **29** 673, 1925

65 Levaditi, C Sur l'état de la cytase dans le plasma des animaux normaux, *Ann Inst Pasteur* **15** 894 (Dec) 1901

66 Delrez, L, and Govaerts, P L'intervention des globulines dans l'élimination des microbes injectés dans la circulation, *Compt rend Soc de biol* **81** 53 (Jan 26) 1918

67 Govaerts, P Le rôle des plaquettes sanguines dans l'immunité naturelle, *Compt rend Soc de biol* **82** 927 (May 31) 1919, Effets de l'injection des plaquettes lavées sur l'élimination des microbes circulant dans le sang, *ibid* **85** 745 (Oct 8) 1921

The thrombocytosis in infectious diseases associated with the presence of numerous small, easily agglutinating platelets constitutes a significant factor in the causation of spontaneous thrombosis and embolism at times observed in these conditions

*Postoperative Thrombocytosis*—Following surgical operations the platelet count manifests a definite behavior, illustrated in the case of patient 44 (table 10 and chart 3) There is usually a decrease in the total count during the first twenty-four hours postoperatively After this point the platelets increase in number, reaching the maximum level toward the end of the second week, and then gradually returning to normal The entire cycle occupies about three weeks The differential platelet formula is abnormal throughout, owing to the presence of increased numbers of small forms This deviation from the normal in

TABLE 10—*Postoperative Differential Platelet Count*

Patient	Sex	Age	Plate lets per Cu Mm	Differential Platelet Formula (In Percentage)				Diagnosis
				Group 1	Group 2	Group 3	Group 4	
44	I	41	342,000	43.0	51.0	6.0		24 hours after cholecystectomy Sixteenth postoperative day
			879,000	59.2	39.1	1.9		
45	F	20	367,000	62.5	35.2	2.3		24 hours after thyroidectomy Tenth postoperative day
			725,000	60.0	33.0	7.0		
46	F	45	480,000	22.0	70.0	8.0		Amputation of foot, preoper- ative count Thirteenth postoperative day
			901,000	69.2	22.8	6.0	2.0	

the morphologic picture of the platelets persists until the total count has returned to normal, which is usually until the end of the third week postoperatively

The postoperative behavior of the total platelet count was first described in detail by Hueck<sup>68</sup> and has subsequently been confirmed by other investigators Galloway<sup>69</sup> noted a similar behavior of the platelets following fractures of the long bones, and Dawbarn, Earlam and Evans<sup>70</sup> observed a corresponding swing of the platelets following

68 Hueck, H Ueber Untersuchungen der Eiweisskörper des Blutes, sowie Blutplättchenzahlungen, besonders nach Operationen, Deutsche med Wchnschr **51** 1869 (Nov 6) 1925, Blutplättchen-Untersuchungen bei chirurgischen Erkrankungen, Deutsche Ztschr f Chir **192** 322, 1925, Blutplättchenveränderungen nach Operationen, München med Wchnschr **73** 173 (Jan 22) 1926

69 Galloway, J F The Blood-Platelets After Fracture, Lancet **1** 1082 (May 16) 1931

70 Dawbarn, R Y, Earlam, F, and Evans, W H The Relation of the Blood Platelets to Thrombosis After Operation and Parturition, J Path & Bact **31** 833 (Oct) 1928

partuition On the other hand, Rosenbaum,<sup>71</sup> employing Fomic's method for counting platelets, failed to observe postoperative thrombocytosis following operations on women for various types of goiter, in fact, there was frequently a considerable drop in the platelet count, persisting until the succeeding menstrual period, which was at times unusually severe This, however, is at variance with my observations on a patient with thyrotoxicosis (patient 45) who after thyroidectomy exhibited definite thrombocytosis, reaching a maximum level on the tenth postoperative day

The postoperative deviation from the normal in the total and differential platelet counts creates a condition favoring the development of

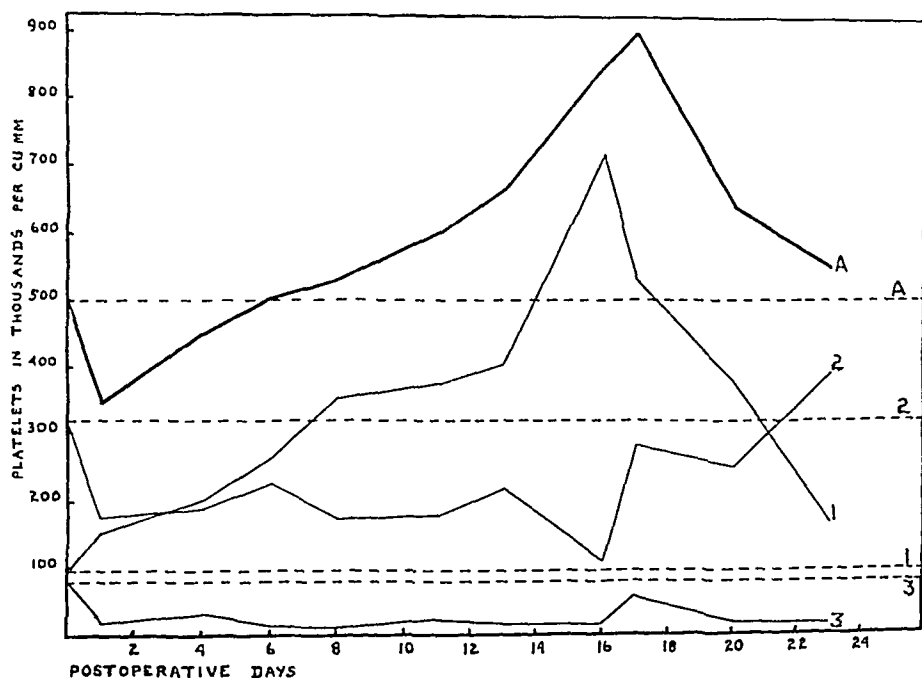


Chart 3 (patient 44) —Behavior of platelets postoperatively (following cholecystectomy)

spontaneous thrombosis and embolism There is considerable evidence indicating that the presence of an increased platelet count is frequently associated with an increased tendency to the development of spontaneous venous thrombosis, or thrombophilia Rosenthal,<sup>72</sup> for instance, observed

71 Rosenbaum, B N Ueber das Verhalten der Blutplättchen bei Struma in der Vor- und Nachoperationsperiode, mit besonderer Berücksichtigung derselben zur Menstruationszeit, *Zentralbl f Chir* **51** 2580 (Nov 22) 1924

72 Rosenthal, N Clinical and Hematologic Studies on Banti's Disease I The Blood Platelet Factor with Reference to Splenectomy, *J A M A* **84** 1887 (June 20) 1925

certain types of splenic anemia in which the thrombocytosis following splenectomy was nearly always associated with widespread thrombosis, often ending fatally. Block and Rake<sup>59</sup> noted that in certain cases of active pulmonary tuberculosis the rise in the platelet count may be associated with spontaneous venous thrombosis. The tendency to non-malignant thrombosis in patients with cancer was ascribed by Naegeli<sup>29</sup> to the frequently associated thrombocytosis. Spontaneous thrombosis in patients with polycythaemia vera, especially in those under phenylhydrazine therapy, was attributed by Jurgens and Bach<sup>18</sup> to the associated elevation in the platelet count. Jagic and Klima<sup>73</sup> noted spontaneous venous thrombosis associated with the thrombocytosis following severe acute hemorrhage. Postinfectious spontaneous venous thrombosis is usually associated with the thrombocytosis observed during convalescence. Postoperatively, the clinically observed thrombosis usually occurs at the height of the rise in the number of platelets, i.e., toward the end of the second week. An important feature of the postoperative thrombocytosis is the presence of numerous small platelets which agglutinate readily. The agglutinability of the platelets, which is dependent on the magnitude of their negative electrical charge (Starlinger and Sametnik<sup>74</sup>), is still further increased by a number of postoperative changes in the blood plasma, such as an increase in fibrinogen and globulin (Lohr<sup>75</sup>) and an increase in glycolysis and in the hydrogen ion concentration of the blood (Jurgens<sup>21</sup> and Stuber and Lang<sup>76</sup>). These factors bring about a lowering of the electrostatic charge of the platelets, thereby decreasing their reciprocal electrostatic repulsion and favoring their agglutination. The thrombocytosis and the associated morphologic changes in the platelets therefore, constitute important postoperative changes in the blood and are significant factors in the pathogenesis of postoperative thrombosis and embolism.

*Miscellaneous Diseases*—Essentially normal total and differential platelet counts were observed in a patient with anaphylactoid purpura and in one with hemophilia. In chronic nephritis the total count is reduced, the differential formula is at times abnormal, owing to the

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73 Jagic, N., and Klima, R. *Klinik und Therapie der Blutkrankheiten* ed 2 Berlin, Urban & Schwarzenberg, 1934.

74 Starlinger, W., and Sametnik, S. Ueber die Entstehungsbedingungen der Thrombose, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* **39** 152, 1927.

75 Lohr, W. Ueber Allgemeinreaktionen des Körpers bei der Wundheilung nichtinfizierter Wunden und unkomplizierter Frakturen, *Deutsche Ztschr. f. Chir.* **183** 1, 1923.

76 Stuber, B., and Lang, K. Zur Pathogenese und Therapie der Thrombose, *Klin. Wchnschr.* **9** 1113 (June 14) 1930.

presence of increased numbers of small platelets Doenecke<sup>77</sup> also found reduced numbers of platelets in chronic nephritis In a patient with hemochromatosis the thrombopenia was associated with an extremely abnormal differential formula due to the presence of numerous large and giant platelets Biopsy on bone marrow, performed by Dr William Dameshek, revealed hypoplasia of the megakaryocytes An essentially normal total platelet count was found in a patient with scurvy who had been under treatment for a short time, the abnormal differential formula due to the presence of many small platelets was suggestive of a recent preexisting thrombopenia

TABLE 11—*Differential Platelet Count in Miscellaneous Diseases*

Patient	Sex	Age	Platelets per Cu Mm	Differential Platelet Formula (in Percentage)				Comment	Diagnosis
				Group 1	Group 2	Group 3	Group 4		
47	F	32	471,000	15.3	70.3	13.7	0.7		Purpura rheumatica
48	M	70	355,000	9.3	42.6	47.4	0.7		Senile purpura
49	M	13	541,000	18.8	60.0	19.4	1.9		Hemophilia
50	M	46	211,000	16.0	46.0	28.0			Malignant nephrosclerosis
51	F	30	300,000	24.0	47.0	27.0	2.0		Malignant nephrosclerosis
52	F	51	224,000	56.0	40.0	1.0	3.0		Chronic glomerulo nephritis
53	M	15	295,000	26.6	61.1	11.2	1.2		Celiac disease
54	M	59	257,000	4.5	39.1	54.3	2.1	Many large and giant platelets	Hemochromatosis
55	F	50	423,000	70.9	25.2	3.9			Scurvy (partly treated)

#### THE AGE OF PLATELETS

Because of the short life cycle of the platelets (several days, according to Duke<sup>78</sup>), it has been rather difficult to establish satisfactory criteria for their maturity or immaturity Basophilia of the cytoplasm of the platelets is said to indicate immaturity (Mackay<sup>10</sup> and Pappenheim<sup>79</sup>) Studies of the tinctorial features of the platelets, however, have yielded rather confusing results The morphologic characteristics of the platelets, on the other hand, do offer some definite criteria as to their age Degkwitz<sup>9</sup> noted that many large and giant platelets appeared

77 Doenecke, F Ueber das Verhalten der Blutplättchen bei echter Uramie, Zentralbl f inn Med **53** 580 (April 30) 1932

78 Duke, W W Causes of Variation in the Platelet Count Experimental Results Showing the Effect of Diphtheria Toxin, Benzol and Tuberculin on the Platelet Count in Rabbits, Arch Int Med **11** 100 (Jan) 1913

79 Pappenheim, A Morphologische Hamotologie, Leipzig, Werner Klinkhardt, 1919

during the regenerative phases in conditions such as infections and loss of blood and during ultraviolet irradiation with a quartz mercury vapor lamp Doenceke,<sup>83</sup> Stahl<sup>80</sup> and Hoiwitz<sup>81</sup> maintained that the larger platelets are immature forms There is considerable evidence, however, that the smaller types, those belonging to group 1, are the juvenile platelets From the observations presented in tables 3 to 11 it is apparent that during the regenerative phase the form exhibiting the greatest relative and absolute increase is usually the small platelet Boshamer<sup>82</sup> and Firket<sup>83</sup> concluded from their experiments of injecting saponin into animals that the small platelets are the young forms A similar opinion was expressed by Jurgens and Naumann,<sup>20</sup> Flossner,<sup>84</sup> Preiss<sup>85</sup> and Lampert<sup>86</sup> Further support for this view is offered by the morphologic changes of the platelets following the injection of epinephrine hydrochloride Epinephrine causes a mobilization of the formed blood elements in the peripheral circulation by bringing about a redistribution of the blood contained in the inactive blood depots of which the spleen represents a reservoir of the first order (Dameshek<sup>87</sup> and Rein<sup>88</sup>) That the spleen is a reservoir of platelets as well as of red cells has been shown by Bedson and Johnston<sup>89</sup> and Binet and Kaplan<sup>90</sup> After the injection of epinephrine hydrochloride the volume of the spleen may become smaller by 12 per cent (Paffenholz and Schurmeyer<sup>91</sup>), and

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80 Stahl, R Ueber die Notwendigkeit prinzipieller Berücksichtigung der Blutplättchen bei klinischen Blutuntersuchungen, München med Wchnschr **68** 667 (June 3) 1921

81 Horwitz, S Zur Frage der physiologischen Thrombocytenzahl, Klin Wchnschr **12** 705 (May 6) 1933 Footnote 47

82 Boshamer, K Ueber Zahlung, Resistenz und Neubildung von Blutplättchen Ztschr f d ges exper Med **48** 631, 1925-1926

83 Firket, J Recherches sur la regeneration des plaquettes, Compt rend Soc de biol **87** 84 (May 27) 1922

84 Flossner, O Beobachtungen und Zahlung von Blutplättchen, Ztschr f Biol **77** 113, 1922

85 Preiss, W Ueber die physiologische Zahl und Morphologie der Blutplättchen, Ztschr f d ges exper Med **84** 810, 1932

86 Lampert, H Die physikalische Seite des Blutgerinnungsproblems und ihre praktische Bedeutung, Leipzig, Georg Thieme, 1931

87 Dameshek, W Physiology of the Spleen, in Piersol, G M Cyclopedia of Medicine, Philadelphia, F A Davis Company, 1934

88 Rein, H Die Blutreservoir des Menschen, Klin Wchnschr **12** 1 (Jan 7) 1933

89 Bedson, S P, and Johnston, M E Further Observations on Platelet Genesis, J Path & Bact **28** 101, 1925

90 Binet, L, and Kaplan, M Mobilisation des plaquettes par l'adrenaline Plaquettose par splenocontraction adrenale, Compt rend Soc de biol **97** 1659 (Dec 17) 1927

91 Paffenholz, W, and Schurmeyer, A Änderungen der Milz- und Lebergrosse im Röntgenbild unter verschiedenen Kreislaufbedingungen, Klin Wchnschr **10** 2076 (Nov 7) 1931



under unusual circumstances, as in the presence of splenomegaly, that organ may lose one third of its original volume (Levy<sup>92</sup>)

Table 12 shows the changes in the total and differential platelet counts following the subcutaneous injection of 1 cc of epinephrine hydrochloride. It is apparent from this table that a characteristic feature of thrombocytosis due to epinephrine is the appearance of increased numbers of large platelets. These additional thrombocytes come from inactive blood reservoirs, where normally hematopoiesis does not occur. They must consequently represent platelets that have remained inactive in the blood depots, where many of them matured, and that were forced into the general circulation after the injection of epinephrine hydrochloride, they are, therefore, older or senile forms. This is in agreement with the observations of Lampson,<sup>93</sup> who noted that in polycythemia due to epinephrine the red cells show none of the usual reactions of

TABLE 12—*Behavior of Platelets Before and After Injection of Epinephrine Hydrochloride*

	Plate lets per Cu Mm	Differential Platelet Formula (in Percentage)				Diagnosis
		Group 1	Group 2	Group 3	Group 4	
Before injection	445,000	26.0	61.5	8.0	3.5	Normal
After injection	604,000	21.9	70.1	8.0	0	
Before injection	252,000	25.0	55.0	18.0	2.0	Bronchial asthma (during seizure)
After injection	407,000	27.8	46.7	22.9	2.6	
Before injection	70,000	33.3	61.3	5.4	0	Chronic thrombocytopenic purpura
After injection	120,000	26.0	62.5	11.5	0	
Before injection	179,000	63.0	34.0	3.0	0	Aleukemic lymphatic leukemia
After injection	220,000	56.0	43.0	1.0	0	
Before injection	252,000	32.8	50.4	16.8	0	Aleukemic myelogenous leukemia
After injection	518,000	24.6	59.2	16.2	0	
Before injection	402,000	61.8	35.2	3.0	0	Catarrhal jaundice
After injection	575,000	28.5	68.0	3.0	0.5	

young erythrocytes. These observations on the effect of epinephrine, therefore, corroborate the view that the larger platelets represent more mature thrombocytes.

#### SUMMARY AND CONCLUSIONS

A method for studying the morphologic picture of the platelets in fresh wet preparations is described. It permits a simultaneous enumeration of the total thrombocyte content.

The behavior of the total and differential platelet counts in a number of important clinical conditions is presented and the significance of the deviations from the normal discussed.

<sup>92</sup> Levy, R. Zur Operation grosser Milztumoren, *Arch. f. klin. Chir.* **170** 188, 1932.

<sup>93</sup> Lampson, P. D. The Role of the Liver in Acute Polycythemia. A Mechanism for the Regulation of the Red Corpuscle Content of the Blood, *J. Pharmacol. & Exper. Therap.* **7** 169 (July) 1915.

The normal platelets can be differentiated into four groups according to size: group 1, consisting of platelets 1.8 microns in diameter; group 2, consisting of platelets 2.5 microns in diameter; group 3, consisting of platelets 3.6 microns or more in diameter; and group 4, consisting of irregular-shaped platelets. In normal persons 18.6 per cent of all the circulating platelets belong to group 1, 63.3 per cent to group 2, 17.4 per cent to group 3 and 0.7 per cent to group 4.

In conditions associated with thrombocytosis and at times in those associated with thrombopenia, the deviation from the normal in the differential platelet formula is usually due to an absolute or relative increase in the number of small platelets, i.e., those belonging to group 1. The presence of increased numbers of the larger types of platelets is often associated with intense regenerative activity, abnormal function or hypoplasia of the megakaryocytes in the bone marrow.

Normally functioning platelets are usually normal morphologically. Functionally, the smaller platelets are much more active than the larger types. The small juvenile platelets possess high agglutinating powers, and their presence in large numbers constitutes a significant factor in the causation of spontaneous thrombosis in conditions associated with thrombocytosis.

# Progress in Internal Medicine

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## BLOOD

A REVIEW OF THE RECENT LITERATURE

RAPHAEL ISAACS, M D

CYRUS C STURGIS, M D

FRANK H BETHELL, M D

AND

S MILTON GOLDHAMER, M D

ANN ARBOR, MICH

In selecting articles to include in this second review of hematology, it has been the policy to consider only those which have a bearing on the recent advances in this field. It has not been possible, nor would it be advantageous, to present a summary of all papers which have been written during the year ending Jan 1, 1935. If any essential articles have been omitted, we present our apologies. As a result of this plan, it may appear as though too much space has been devoted to some phases of the subject and too small amounts to others, but under the circumstances this could not be avoided.

## PERNICIOUS ANEMIA

### ETIOLOGY

The most important discussions centering about the etiology of pernicious anemia during the past year are primarily concerned with the nature of the intrinsic and the extrinsic factor, the site of the interaction between the two and the relation between them, and the etiology not only of pernicious anemia but also of some related conditions, such as sprue and the tropical macrocytic anemias.

Castle,<sup>1</sup> in his lecture before the Harvey Society, gave an excellent resumé of the knowledge concerning the present views in regard to the cause of pernicious anemia and included a list of the more important recent articles dealing with this topic and with related macrocytic anemias. He reiterated his former theory that Addisonian pernicious anemia is due to a lack of the gastric factor in the stomach. Goldhamer and

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From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan

1 Castle, W B. The Etiology of Pernicious and Related Macrocytic Anemias, *Science* **82** 159, 1935

his associates<sup>2</sup> expressed the belief that the change may be relative rather than absolute

The nature of the intrinsic factor is still undetermined, although, according to Castle, it is known not to be hydrochloric acid or any of the recognized ferments of the gastric secretion. According to him it is thermolabile, as it is destroyed by heating for one-half hour at from 70 to 80 C. It is not present in the saliva or in the duodenal contents.

Castle also stated that the nature of the extrinsic factor is likewise unknown, although it has a wide distribution, for it is known to be present in beef muscle, eggs, autolyzed yeast, rice polishings, wheat germ and liver. This substance is thermostable, as it is not destroyed in autolyzed yeast when subjected to an autoclave pressure of 15 pounds (68 Kg.) for five hours.

Efforts have been made to ascertain the site of the interaction between the food and the gastric factors, but complete information concerning this is still lacking. Castle has not been able to form a thermostable substance similar to that found in liver by the incubation of beef muscle and normal gastric secretions *in vitro*. He has also been unable to determine to his satisfaction if the two factors, when incubated and then administered parenterally, can produce an effect which is comparable to that obtained by the oral administration of a material which is potent against pernicious anemia. According to him, confusing results may be obtained because the parenteral administration of substances containing proteins or their derivatives may produce a reticulocyte response which is not necessarily associated with an increase in the total red blood cell count or with clinical improvement of the patient.

In explaining the occasional response of a patient with pernicious anemia to large doses of the extrinsic factor alone, in the form of autolyzed yeast, he expressed the belief that it is associated with a spontaneous increase in the amount of intrinsic factor in the gastric secretions.

Miller and Rhoads<sup>3</sup> have contributed an experimental study dealing with the cause of the macrocytic anemias which may have an important bearing on the theories concerning these conditions. They considered that previously there has been no reported instance in which the major pathologic and physiologic changes of pernicious anemia have been

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2 Goldhamer, S. M., Isaacs, R., and Sturgis, C. C. The Quantitative Relationship Between the Amount of the "Intrinsic Factor of Castle" and the Maturation of Red Blood Cells in Patients with Pernicious Anemia, *J. Clin. Investigation* **14** 708, 1935.

3 Miller, D. K., and Rhoads, C. P. The Experimental Production of Loss of Hematopoietic Elements of the Gastric Secretion and of the Liver in Swine with Achlorhydria and Anemia, *J. Clin. Investigation* **14** 153, 1935.

produced as a disease syndrome in a lower animal. By feeding to swine a modification of a diet that produces black tongue in dogs, they have produced a condition characterized by hematologic, lingual and gastrointestinal changes which are similar to those seen in cases of pernicious anemia. This diet was given to 15 animals, and macrocytic anemia developed in 9, of these, 7 were found to have achlorhydria, whereas hydrochloric acid had been present in the gastric secretions before the experiment. Lesions of the lingual, buccal or pharyngeal mucous membranes developed in all 9. It was also demonstrated by the method of Castle that there was a loss of the intrinsic factor in the gastric secretions. Furthermore, when extracts were prepared from the livers of these animals and given to patients with pernicious anemia, it was found that they did not contain the antianemic substance. A number of their animals, which were subjected to the same experimental procedures, were found to have microcytic anemia, which is somewhat difficult to explain. The general similarity, however, between the disease thus produced in swine and pernicious anemia, sprue and tropical anemia was impressive. It suggested to these observers that these conditions are due to a common cause which may be the result of the lack of intake of, or an inability to utilize, some poorly defined dietary constituent. While there may be some objections to this rather broad statement, it must be admitted that a disease has been produced experimentally in animals which simulates pernicious anemia in many respects.

Observations which can be correlated with those just cited have been made by Goodman, Geiger and Claiborn<sup>4</sup>. They determined the amount of the antianemic factor in the livers of swine after gastrectomy had been performed for periods varying from two to six months. An extract was prepared from the livers of these animals and given orally to patients with pernicious anemia. They concluded that the antianemic potency was diminished and that this may be detected as early as the third month after gastrectomy.

Meulengracht<sup>5</sup> and his collaborators have directed their attention toward localizing the area of the stomach which secretes the antianemic factor and determining if it is also present in the duodenum. It was first found that the glands of the cardiac, fundic and pyloric regions were anatomically distinct in swine. By careful dissection of the

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4 Goodman, L., Geiger, A. J., and Claiborn, L. N. Anti-Anemia Potency of Liver After Gastrectomy in Swine, *Proc Soc Exper Biol & Med* **32** 810, 1935.

5 Meulengracht, E. Continued Investigations on the Presence of the Anti-Anaemic Factor in Preparations of Dried Stomach Substance from the Cardia, Fundus and Pylorus Regions. IV Preparations from the Cardia Region, *Acta med Scandinav* **85** 50, 1935, V Preparations from the Duodenum, *ibid* **85** 79, 1935.

stomachs of pigs and the administration of the material obtained to patients with pernicious anemia, it was found that the material containing glands of the fundus was inactive whereas that from the pyloric region was exceedingly potent. Tissue from the cardiac region of the stomach, while anatomically similar to that from the pyloric region, had only a slight potency. This was attributed to the sparsity of the glands in this area. It was also determined that the glands of Brunner in the duodenum had the same activity as those of the pylorus. It was suggested that the duodenal glands may assume the function of the glands of the pylorus in man when gastric atrophy develops or when the pylorus is resected. A theory is thus provided to explain why pernicious anemia does not develop under the aforementioned clinical conditions.

Jones, Benedict and Hampton<sup>6</sup> studied the gastric mucosa in 5 cases of pernicious anemia before and after treatment by gastroscopic and roentgenologic examinations by direct observation at laparotomy and by histologic examination of biopsy material. Contrary to most observers these investigators found that atrophy of the mucosa was not an invariable accompaniment of the disease, although it occurred, particularly during a relapse. After specific therapy, evidence of atrophy or hypertrophy tended to disappear. This was interpreted as an epithelial change rather than the healing of a chronic inflammatory process. The apparent return to normal from a grossly hypertrophic condition represents a subsidence of a chronic gastritis.

Wakerlin<sup>7</sup> reported the presence of an antianemic principle in normal human urine. This material, when injected into pigeons, increases the reticular material in the red blood cells in a manner similar to that observed after the use of the antianemic material present in liver. Wakerlin prepared an extract from urine by a procedure similar to that employed in making liver extracts for parenteral administration. This was given intramuscularly to a patient with pernicious anemia and after thirty-five days of treatment the number of red blood cells had increased from 2,650,000 to 3,640,000 per cubic millimeter and the hemoglobin content from 63 to 83 per cent. These higher levels had not been obtained when liver therapy had been given to the same patient on a previous admission. Additional observations are necessary before definite conclusions can be made concerning the experiment.

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6 Jones, C. M., Benedict, E. B., and Hampton, A. O. Variations in Gastric Mucosa in Pernicious Anemia. Gastroscopic, Surgical and Roentgenologic Observations, *Am J M Sc* **190** 596, 1935.

7 Wakerlin, G. E. Presence of Anti-Pernicious Anemia Principle in Normal Human Urine, *Proc Soc Exper Biol & Med* **32** 1607, 1935.

*Diagnosis*—Minot<sup>8</sup> discussed some aspects of the diagnosis of pernicious anemia which should be emphasized to all practitioners of medicine. He first deplored the fact that so much has been written about therapy during the past eight years that the need of a correct diagnosis has not received the proper attention. In not a few instances both liver and iron preparations are prescribed for a patient with anemia, improvement results, but the physician may never determine which one of these essential drugs are indicated. One hundred cases were studied to determine the relative frequency of the initial symptoms. It was found that in 33 per cent the initial symptom was weakness, in 31 per cent the symptoms were gastro-intestinal and in 26 per cent they were referred to the nervous system and in 10 per cent to the heart. The diagnosis of pernicious anemia was not established in the group until an average of one and three-tenths years after the initial symptoms occurred. In those patients whose earliest symptom was weakness or was cardiac, the diagnosis was recognized earlier than in those with gastro-intestinal or neural symptoms. While the gastro-intestinal or nervous manifestations may be mild, they may be present a long time before anemia is apparent, and it is not until the latter develops that the correct diagnosis is recognized.

Minot also emphasized the fact that there is frequently a history of vague gastro-intestinal symptoms of long standing in patients with pernicious anemia which can be attributed in part to gastric achlorhydria or to manifestations of the "deficient state." Furthermore, symptoms which suggest dysfunction of the gallbladder are not uncommon, and if they persist after proper treatment, it is additional evidence that they are dependent on disease of the gallbladder.

Mention is also made in Minot's article that the excess pigment metabolism which results in the lemon yellow color of the patient and also splenomegaly are now uncommon as compared to their previous incidence. The comparative rarity of both these conditions may possibly be due to the fact that modern treatment causes the anemia to disappear promptly, and as a result the excess pigment metabolism persists for only a short time. Certain concomitant conditions, such as cancer of the stomach, cirrhosis of the liver, myxedema and diabetes, are not rare in patients with pernicious anemia and should not cause the latter condition to be overlooked. It should be recognized that infections, an inadequate diet and possibly other factors may be the precipitating cause of pernicious anemia.

#### GASTRIC JUICE

Since Castle demonstrated the presence of the "intrinsic" factor in the gastric juice, the study of this secretion has become of increasing

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<sup>8</sup> Minot, G. R. Some Aspects of the Diagnosis of Pernicious Anemia, *M Clin North America* 18: 935, 1935.

importance. Excellent reviews of the literature concerning gastric juice up to 1935 have been published<sup>9</sup>. It is now generally accepted that pernicious anemia is associated with achlorhydria, and it has been shown that the intrinsic factor is present in decreased amounts in the gastric juice of patients with pernicious anemia.

Several interesting experiments have been performed with gastric juice. Two groups of investigators working independently have noted the increased potency of liver extract by incubation with normal human gastric secretion<sup>10</sup>. On the basis of the theory that a hematopoiesis-stimulating substance is formed from the interaction of the extrinsic and the intrinsic factor and stored in the liver, it has been demonstrated that by removal of the stomach in swine the antianemic potency of the liver is gradually diminished<sup>4</sup>. The effectiveness of gastric juice injected intramuscularly in cases of pernicious anemia has been confirmed again<sup>11</sup>. A simple animal test to determine the presence or absence of the intrinsic factor in gastric secretion has been devised<sup>12</sup>. When normal gastric juice is filtered and neutralized with sodium bicarbonate and injected into white rats maintained on a milk and bread diet, a reticulocyte response is noted on from the third to the fifth day. Heated gastric secretion obtained from patients with pernicious anemia and that obtained from dogs are ineffective. The experiments with the secretion from dogs confirmed the contention that powdered dog stomach is of no value in the treatment of pernicious anemia. The gastric contents of patients with chronic microcytic anemia was effective.

The nature of the intrinsic factor is thought by some to be an enzyme and by others to be a hormone. The latter view, propounded by Morris, has recently been emphasized<sup>13</sup>.

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9 Friedenwald, J., Morrison, T. H., and Morrison, S. Modern Conception Concerning Certain Gastric Affections. Disturbances of the Gastric Secretion and the Production of Various Types of Anemia and Certain Other Affections, *Internat M Digest* **26** 53, 1935. Klumpp, T. S., and Koletsky, S. Relation of Gastric Secretion to Hematopoiesis, *Ann Int Med* **8** 991, 1935.

10 (a) Fouts, P. J., Helmer, O. M., and Zerfas, L. G. Quantitative Studies on Increased Potency of Liver Extract by Incubation with Normal Human Gastric Juice, *Ann Int Med* **8** 790, 1935. (b) Reimann, F., Breuer, A., and Langecker, H. Ueber die Wirksamkeitssteigerung der Leber nach Behandlung mit tierischem Magen, Magenschleimhaut und Extrakt aus Magenschleimhaut (künstlichen Magensaft). Untersuchungen zur Leberwirkung bei der Anaemia perniciosa, *Ztschr f klin Med* **127** 438, 1934.

11 Tochowicz, L. Ueber den therapeutischen Wirkungsmechanismus des par-enteral eingeführten, verdichteten, normalen Magensaftes (Addisin) im Verlaufe der Biermerschen Krankheit, *Folia haemat* **53** 16, 1934.

12 Singer, Karl. Ueber eine tierexperimentelle Methode zum Nachweis des Castle-Prinzips des Magensaftes und deren klinische Bedeutung, *Klin Wchnschr* **14** 200, 1935.

13 Braun, B. Der Mechanismus der therapeutischen Einwirkung des Castle-schen Prinzips bei der perniziösen Anämie, *Folia haemat* **53** 27, 1934.



Studies have been made of the gastric juice of children<sup>14</sup> and of adults<sup>15</sup> with types of anemia other than pernicious anemia. According to Ogilvie, the constituents of the gastric secretion with the exception of free and total acid, are normal in children with anemia. Defective secretion of hydrochloric acid and anemia appear to be closely related. Fouts and his co-workers found no alteration in the gastric juice of adults with anemia resulting from chronic hemorrhage. In cases of idiopathic hypochromic anemia, anemia associated with pregnancy and endocrine dysfunctions, anemia due to dietary deficiency and anemia refractive to medication, both the enzyme content and the acidity are reduced. The most consistent decreases in the enzyme content and acidity are seen in cases of idiopathic hypochromic anemia. These authors expressed the belief that if anacidity is present and enzymes are absent, the condition is permanent.

A few years ago Morris postulated that polycythemia was the result of overstimulation of hematopoietic activity by increased secretion of addisin. He advised constant gastric drainage with removal of the excess amount of the hormone as treatment for this condition. The experiments of Morris have been repeated by Briggs and Oerting,<sup>16</sup> who expressed the opinion that this type of therapy is most effective in cases of polycythaemia vera.

#### MANIFESTATIONS DUE TO LESIONS IN THE SPINAL CORD AND BRAIN

Although the symptoms and signs referable to degeneration of the spinal cord are regarded as a part of the disease process, involvement of the brain with its associated mental symptoms is not necessarily considered as a part of pernicious anemia.<sup>17</sup> The etiology of the changes in the nervous system remains obscure. It is believed by some, as a result of experimental evidence, that the manifestations in the spinal cord may result from a vitamin deficiency which is chronic rather than acute.<sup>18</sup> Others still maintain that there is a specific neurotoxin due

14 Ogilvie, J. W. The Gastric Secretion in Anaemia, *Arch Dis Childhood* **10** 143, 1935.

15 Fouts, P. J., Helmer, O. M., and Zerfas, L. G. Gastro-Intestinal Studies. Gastric Juice in Anemias Other Than Pernicious Anemia, *Am J Digest Dis & Nutrition* **1** 677, 1934.

16 Briggs, J. F., and Oerting, H. Influence of Gastric Lavage on Familial and Non-Familial Erythremia, *Minnesota Med* **18** 499, 1935.

17 Osgood, C. W. Mental Changes Associated with Pernicious Anemia, *J A M A* **104** 2155 (June 15) 1935. Preu, P. W., and Geiger, A. J. Symptomatic Psychoses in Pernicious Anemia, *Ann Int Med* **9** 766, 1935.

18 Gildea, M. C. L., Castle, W. B., Gildea, E. F., and Cobb, S. Neuro-pathology of Experimental Vitamin Deficiency. Report of Four Series of Dogs Maintained on Diets Deficient in B Vitamins, *Am J Path* **11** 669, 1935.

to a disturbance in lipid metabolism or that the changes in the central nervous system are related to the anemia. Opposition to the latter view has been brought forward by observers who concluded from their research work with gastric juice that anemia and the changes in the spinal cord may occur together but that they are independent diseases<sup>19</sup>

Involvement of the spinal cord has been reported in as high as 90 per cent of the cases of pernicious anemia, and the general consensus is that more than 70 per cent of patients with this condition exhibit neurologic manifestations. Manifestations of cerebral involvement have been noted in approximately 60 per cent of the persons suffering from pernicious anemia. The incidence of involvement of the central nervous system appears to be increasing since the advent of antianemic therapy.

The most common neurologic symptoms are numbness and tingling of the extremities, coldness, ataxia, loss of finer coordination of the fingers and disturbances of the bladder. The character of the signs depends on whether the changes in the posterior or in the lateral columns of the spinal cord predominate. The reflexes may be increased, decreased or lost. Disturbance in the vibratory sensation is the outstanding sign. There does not appear to be any specific mental picture<sup>20</sup> and, as stated before, it is the opinion of some authors that the manifestations of cerebral involvement are independent of the disease process of pernicious anemia.

Conclusions drawn from the benefits of therapy must be guarded, as it is known that there may be spontaneous variations in the intensity of the neurologic manifestations without treatment. Improvement in symptoms and objective arrest in signs have been reported with the administration of liver, parenteral liver extract,<sup>21</sup> desiccated stomach brain substance and iron, the use of a diet high in vitamins, removal of foci of infection and reeducation.<sup>22</sup> Manifestations referable to the

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19 Salus, F, and Reimann, F. Das Castlesche Ferment und die funikuläre Spinalerkrankung. Ein Beitrag zur Pathogenese des nervösen Krankheitssyndroms (VI Untersuchungen zur Leberwirkung bei der Anaemia perniciosa), *Klin Wchnschr* **13** 986, 1934.

20 Bowman, K. M. Psychoses with Pernicious Anemia, *Am J Psychiat* **92** 371, 1935.

21 (a) Strauss, M. B., Solomon, P., Schneider, A. J., and Patek, A. J., Jr. Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia. The Complete Arrest of the Lesion with Parenteral Liver Therapy, *J A M A* **104** 1587 (May 4) 1935. (b) Sanford, C. H. Pernicious Anemia with Normal Blood Picture, *Ann Int Med* **9** 189, 1935. (c) Farquharson, R. F. The Importance of Rest and Liver Therapy in the Treatment of Subacute Combined Degeneration of the Cord, *Canad M A J* **33** 473, 1935.

22 (a) Brain, W. R. Subacute Combined Degeneration, *Brit M J* **2** 1056, 1935. (b) Cohen, H. Subacute Combined Degeneration of the Spinal Cord, *Lancet* **1** 1291, 1935.

posterior columns respond more readily than those due to lesions of the lateral columns. It is also to be noted that improvement may not be expected for several months after intensive therapy has been instituted. It is claimed that better results are obtained in younger persons<sup>22b</sup> and in those patients in whom the involvement of the central nervous system has been of short duration<sup>21c</sup>. If the cerebral changes are a result of the disease process, some improvement may be anticipated, however, if a psychosis exists independent of pernicious anemia, no improvement can be expected with antianemic therapy.

#### BLOOD

Emerson and Helmer<sup>23</sup> found that the condition of acid-base equilibrium in 29 patients with pernicious anemia was independent of the clinical status. There was an apparent tendency toward alkalosis, but the authors considered the acid-base equilibrium as normal. The  $p_H$  varied over a range twice as broad as in normal persons. The daily administration of hydrochloric acid produced no appreciable change in the acid-base equilibrium of the blood in patients with pernicious anemia.

Watson<sup>24</sup> isolated coproporphyrin I from the feces of 2 patients with pernicious anemia. After liver therapy, the amount was significantly decreased to the amount found in normal persons and in patients with other types of anemia.

The color index of serum, as determined by Schmehle and Schmid<sup>25</sup> with the step photometer, was increased in cases of severe pernicious anemia but decreased rapidly after therapy. Relapse is less likely to occur in patients whose color index is normal than in those in whom the index remains high in spite of normal erythrocyte values. Pernicious anemia is contrasted to "achylic anemia," in which the index value is subnormal.

Wintrobe and Shumacker<sup>26</sup> called attention to certain similarities between the blood of the fetus and that of patients with pernicious anemia in whom an induced remission has been instituted with potent therapy. In the fetus there is macrocytosis, reticulocytosis and nucleated

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23 Emerson, C. P., Jr., and Helmer, O. M. Reaction ( $p_H$ ) and Carbon Dioxide Content of Venous Plasma in Pernicious Anemia, *Arch Int Med* **55** 254 (Feb) 1935.

24 Watson, C. J. Concerning Naturally Occurring Porphyrins. Isolation of Coproporphyrin I from Feces of Untreated Cases of Pernicious Anemia, *J Clin Investigation* **14** 116, 1935.

25 Schmehle, E., and Schmid, H. Ueber Serumfarbkurven bei perniziöser und einfach achylischer Anämie, *Klin Wchnschr* **14** 675, 1935.

26 Wintrobe, M. M., and Shumacker, H. B., Jr. Comparisons of Hematopoiesis in Fetus and During Recovery from Pernicious Anemia, Together with Consideration of Relationship of Fetal Hematopoiesis to Macrocytic Anemia of Pregnancy and Anemia in Infants, *J Clin Investigation* **14** 837, 1935.

red blood cells appear in the peripheral circulation. As the time of birth approaches, the blood assumes more of the adult characteristics.

In the bone marrow of the sternum, Isaacs<sup>27</sup> found no simple correlation between the total number of nucleated cells of all types and the peripheral red blood cell count. There was considerable variation in the cellularity of the marrow in different persons. The blood count of 3,000,000 red blood cells per cubic millimeter indicates the point at which the megaloblastic marrow approaches the normal condition. It is at this point that some patients become resistant to specific therapy.

Sanford<sup>21b</sup> emphasized the fact that the blood may be normal in a patient with pernicious anemia, with the involvement limited to the central nervous system. He reported 3 cases in which the response to liver extract was good.

Minot and Castle<sup>28</sup> made an excellent summary of the present knowledge of the behavior of reticulocytes in cases of pernicious anemia in which remissions were induced. In considering the reticulocyte responses to medication, it is important to evaluate the nonspecific or "irritant" effects of certain substances, such as potassium arsenite.

Murphy<sup>29</sup> warned against one placing too great emphasis on comparable reticulocyte responses as he considered that some substances may cause an increase in the reticulocyte count whereas others may not produce this effect although they possess the ability to increase the erythrocyte count.

#### TREATMENT

Wilkinson<sup>30</sup> again emphasized the necessity for the permanent use in cases of pernicious anemia of adequate amounts of a potent stomach or liver preparation. In cases in which there were neurologic symptoms he recommended full doses without a decrease. The prognosis of uncomplicated pernicious anemia is good if these points are observed.

The question of an increase in the potency of kidney and liver after autolysis was reinvestigated by Castle and Strauss,<sup>31</sup> who concluded

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27 Isaacs, R. Bone Marrow Changes (Quantitative) in Patients with Pernicious Anemia During Period of "Reticulocyte" Response, *Tr A Am Physicians* **50** 249, 1935.

28 Minot, G. R., and Castle, W. B. Interpretation of Reticulocyte Reactions Their Value in Determining Potency of Therapeutic Materials, Especially in Pernicious Anemia, *Lancet* **2** 319, 1935. Minot, G. R. Interpretation of Reticulocyte Responses in Pernicious Anemia, *Tr A Am Physicians* **49** 287, 1934.

29 Murphy, W. P. Facts Concerning Treatment of Anemia, *New York State J Med* **35** 973, 1935.

30 Wilkinson, J. F. Treatment of Pernicious Anemia, *Practitioner* **134** 272, 1935.

31 Castle, W. B., and Strauss, M. B. Effect of Autolysis on Potency of Liver in Treatment of Pernicious Anemia, *J A M A* **104** 798 (March 9) 1935.

that the autolyzed liver has less potency than the amounts of material from which it was derived. Conner and McQuiston<sup>32</sup> reported good responses in 3 patients, poor responses in 3 and doubtful but apparently poor responses in 2.

The dietary factor active against pernicious anemia (extrinsic factor of Castle) was found to be present in the white of egg by Miller and Rhoads<sup>33</sup>. While this is compatible with the concept that the extrinsic factor is vitamin B<sub>2</sub> (G), it does not prove it, as white of egg contains many other substances.

Mogensen<sup>34</sup> pointed out that there is a form of pernicious anemia in which there is a deficiency of iron and in which large doses of iron preparations are a necessary supplement to treatment with liver or stomach preparations when the latter are inadequate to produce a complete remission. Sherman and his co-workers<sup>35</sup> confirmed the experiences of other authors in that the feeding of liver alone, without the addition of meat, fruit or vegetables, is effective. They recommended smaller doses than have been used (from 150 to 200 Gm daily). Their experience with powdered liver extract was not good. After from three to four months of treatment, the urobilin in the urine, the blood sugar content and the ability to digest neutral fat and muscle tissue approached normal. They noted improvement in the symptoms referable to the spinal cord after an uninterrupted liver diet.

Scowen and Spence<sup>36</sup> used a concentrated liver extract intramuscularly, from 5 to 10 cc being required to bring about a complete remission. As with other preparations, they found that the interval between maintenance doses varies from patient to patient and in the same patient from time to time.

Decastello<sup>37</sup> found that he could produce hematopoietic improvement in patients by giving a daily enema of 300 cc of urine of healthy persons or of patients with pernicious anemia. Urine from patients with other forms of anemia was ineffective. Decastello considered that the active

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32 Conner, H. M., and McQuiston, J. S. Autolyzed Liver in Treatment of Pernicious Anemia, *Proc. Staff Meet., Mayo Clin.* **10** 740, 1935.

33 Miller, D. K., and Rhoads, C. P. Reticulocyte Response in Guinea Pigs Following Oral Administration of Certain Anti-Anemic Substances, *New England J. Med.* **213** 99, 1935.

34 Mogensen, E. Iron Treatment in Pernicious Anemia, *Ugeskr. f. Læger* **96** 1368, 1934.

35 Sherman, S. I., Semenova, M. P., Alekseev-Berkman, I. A., Shcheglova, A. V., and Shatalova, A. A. Dietetic Treatment of Pernicious Anemia, *Sovet vrach gaz.*, Feb. 28, 1935, p. 295.

36 Scowen, E. F., and Spence, A. W. Concentrated Liver Extract for Parenteral Administration in Pernicious Anaemia, *Brit. M. J.* **1** 246, 1935.

37 Decastello, A. Ueber antianamisch wirksame Substanzen im Harn, *Med. Klin.* **31** 377, 1935.

substance in urine was the same as the "intrinsic factor" of Castle and that it may be present in the blood of patients with pernicious anemia but is not secreted in their stomachs

Wakerlin<sup>7</sup> made a urine concentrate from normal persons and found that it had some hematopoietic effect

Strauss and his co-workers<sup>21a</sup> were able to arrest the progress of the neurologic lesions in 26 patients with pernicious anemia and to prevent their development in 84 other patients by adequate treatment with liver extract intramuscularly. In contrast to this, Straube<sup>38</sup> presented evidence based on a study of his patients which makes him conclude that the neurologic symptoms seen in cases of pernicious anemia cannot be cured or prevented

Tochowicz<sup>11</sup> used concentrated gastric juice (hog or human) and prepared a sterile acetone extract which he gave intramuscularly. A single injection produced a complete remission of all symptoms (except return of normal gastric secretion) for several months. Braun<sup>13</sup> repeated Castle's experiments, using hog gastric juice in 1 patient and human secretion in another, with good responses

Meulengracht<sup>39</sup> found that most of the antianemic property of hog stomach was in the pyloric glandular region. The duodenum also possessed powerful antianemic properties. The glands of Brunner in this region are similar, histologically, to those in the pyloric region of the stomach

Schemensky<sup>40</sup> made an active preparation from dried defatted hog colon, which produced results similar to those produced by liver or stomach tissue, but they were obtained somewhat more slowly

Ungley and James<sup>41</sup> found that yeast products given parenterally were not effective in the treatment of pernicious anemia, which supports

38 Straube, G. Die Nervenstörungen der perniziösen Anämie unter besonderer Berücksichtigung ihrer Beeinflussbarkeit durch die Therapie, *Med. Klin.* **31** 1164, 1935

39 Meulengracht, E. Preliminary Report on Presence of Anti-Anemic Factor in Dried Stomach Preparations from Cardiac, Fundic and Pyloric Portion, Respectively, and from Duodenum. Preparations from Duodenum, *Ugeskr. f. Læger* **97** 725, 1935, Pyloric Glands in Relation to Pernicious Anemia, *Nord. med. tidskr.* **9** 865, 1935, The Glands of the Stomach in Relation to Pernicious Anemia, with Special Reference to the Glands in the Pyloric Region, *Proc. Roy. Soc. Med.* **28** 841, 1935, footnote 5

40 Schemensky, W. Zur Pathologie der perniziösen Anämie. Therapeutische Erfolge mit Verfütterung getrockneten Schweinedickdarmpulvers. Mit einem Anhang: Therapeutische Betrachtungen zur Colitis gravis, *Ztschr. f. klin. Med.* **128** 428, 1935

41 Ungley, C. C., and James, G. V. Effect of Yeast and Wheat Embryo in Anaemias. Nature of Haemopoietic Factor in Yeast Effective in Pernicious Anaemia, *Quart. J. Med.* **3** 523, 1934

the contention that the hematopoietic substance in yeast is more like the extrinsic factor of Castle than liver extract. However, there was no parallel between the vitamin B<sub>2</sub> potency of the yeast extracts and the hematopoietic effects. The response to yeast or wheat germ given by mouth in 10 of 18 patients indicates that some patients retain to a degree the ability to secrete the intrinsic factor.

Mermod and Dock<sup>42</sup> produced lasting remissions in two patients with pernicious anemia by the intravenous injection of 1.5 per cent congo red 4 B in a 6 per cent solution of dextrose, from 60 to 90 cc in from five to ten days. The authors considered the action as one of neutralization of toxic substances.

Dakin and West<sup>43</sup> isolated a hematopoietic material from liver which produced optimal results in doses of 80 mg. The method used by these investigators consists of removal of the inactive material with alcoholic calcium acetate and precipitation of the active material with Reinecke salt in acid solution. The material is salted out with ammonium sulfate and reprecipitated with magnesium sulfate, sodium chloride or flavianic acid. The yield is about 1 per cent of the dry liver extract powder. The material is inactivated by sodium hydroxide, sulfuric acid and salts of heavy metals. Deutsch and Wilkinson<sup>44</sup> found that the antianemic principle of liver extract was not the substance which caused the formation of methemoglobin in hemolyzed blood.

West<sup>45</sup> summarized the present knowledge concerning the chemical nature of the hematopoietically active substance in liver. According to him, the active material forms a precipitate with phosphotungstic acid and with Reinecke's salt. Salts of gold, silver, platinum and mercury, as well as sodium hydroxide and mineral acids, destroy the potency. Heating to 100 C at  $p_H$  5 does not lessen the clinical effect. It is soluble in water, and the partly purified material is soluble in slightly acid 95 per cent alcohol. It is insoluble in ether. The substance does not give a reaction to the biuret test, it contains carbon, hydrogen, oxygen and nitrogen. Phosphorus and sulfur are absent. Kyer<sup>46</sup> found that the active material could be purified by adsorption on charcoal from an acid solution.

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42 Mermod, C, and Dock, W. Colloidal Dye Effective in Treating Pernicious Anemia and Evoking Reticulocytosis in Guinea Pigs, *Science* **82** 155, 1935.

43 Dakin, H. D., and West, R. Observations on Chemical Nature of Hematopoietic Substance in Liver, *J Biol Chem* **109** 489, 1935.

44 Deutsch, W., and Wilkinson, J. F. "Methaemoglobin-Production" Test for Assaying Anti-Anemic Potencies of Liver Extracts, *Brit J Exper Path* **16** 33, 1935.

45 West, R. Antianemic Material of Liver and Stomach, *J A M A* **105** 432 (Aug 10) 1935.

46 Kyer, J. L. Charcoal Adsorption as a Method for the Preparation of a Concentrated Liver Extract, *Proc Soc Exper Biol & Med* **32** 1102, 1935.

For assay of the material, Jacobson<sup>47</sup> injected it into selected guinea-pigs and studied the blood for a reticulocyte response. The responses were quantitative and were expressed in "guinea-pig units." The unit is "the minimal amount of material per kilogram guinea pig, which, after a single intraperitoneal administration, induces a positive reticulocyte response in at least two of three reactive guinea pigs." The phenomenon was confirmed by Miller and Rhoads<sup>33</sup>.

Muller<sup>48</sup> used pigeons to test the hematopoietic activity of liver extract. Injections of potent material caused an increase in the percentage of reticulocytes, but similar responses were obtained from intravenous injections of lysine and leucine, but arginine and histidine gave but indefinite responses. After the administration of liver extract the megablasts of the bone marrow were transformed into more adult red blood cells, but after the administration of lysine or leucine there were an increase and extension of erythroblastic tissue, with numerous megablasts and mitotic figures.

Kamerling,<sup>49</sup> testing Singer's method of evaluating the potency of the Castle principle generated by the action of gastric juice on meat or liver found that similar responses could be elicited by the injection into rats of mixtures of pepsin and hydrochloric acid.

Minot,<sup>50</sup> in the Nobel lecture, emphasized the necessity of giving sufficient potent material, enough to supply, besides the hematopoietic requirements, all the demands of the body for the substance and to fill it adequately with a reserve supply. It is probable that more material is required to improve or to inhibit the progress or development of neurologic symptoms than is necessary to maintain a normal blood count. Minot wisely added that "the physician, however, must do more for his patient than prescribe a proper amount of liver, stomach or the like, he should attend to all aspects of the case and not neglect attention to the individual's manifold problems of thought and action."

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47 Jacobson, B. M. Response of Guinea Pig's Reticulocytes to Substances Effective in Pernicious Anemia. Biologic Assay of Therapeutic Potency of Liver Extracts, *J. Clin. Investigation* **14** 665, 1935, Assay on Guinea Pigs of Hematopoietic Activity of Human Livers, Normal and Pernicious Anemia, *ibid* **14** 679, 1935.

48 Muller, Gullu Lindh. Reticulocyte Responses in the Pigeon Produced by Material Effective and Non-Effective in Pernicious Anemia with Description of the Histologically Different Reactions of the Bone Marrow, *New England J. Med* **213** 1221, 1935.

49 Kamerling, A. W. C. G. Zur Frage der tierexperimentellen Methode Singers zum Nachweis des Castle-Prinzips, *Wien klin. Wchnschr* **48** 1140, 1935.

50 Minot, G. R. Development of Liver Therapy in Pernicious Anemia, *Lancet* **1** 361, 1935.



Stare and Thompson<sup>51</sup> used a purified flavine made from liver in the treatment of patients with pernicious anemia. No hematopoietic response was noted when this was given intramuscularly. Conversion of the flavine of liver extract into photoflavine did not impair its potency.

Liver contains both the hematopoietically active substance and the material which can act as the "extrinsic factor" when acted on by gastric juice. Fouts, Helmer and Zerfas<sup>10a</sup> found that the potency of liver extract could also be increased by digestion with normal human gastric juice but that the final product was not as active as material derived from whole liver under these circumstances. To increase the potency of 4.5 Gm of liver extract satisfactorily, 50 cc or more of gastric juice was necessary.

Goldhamer, Isaacs and Sturgis<sup>2</sup> found that patients with pernicious anemia secreted the intrinsic factor of Castle during relapse, but in greatly diminished quantity. The average total secretion in these patients was only 20 cc per hour as compared with 150 cc in normal persons under the same conditions. Gastric secretion collected from patients with pernicious anemia when used in sufficient amounts and incubated with meat caused an induced remission in 2 patients with pernicious anemia. A third patient responded to intramuscular injections of his own gastric juice.

### MACROCYTIC ANEMIA OTHER THAN PERNICIOUS ANEMIA

In several recent reviews<sup>52</sup> it has been pointed out that macrocytic anemia may be produced by many different factors. It is generally accepted that the interaction of the extrinsic and the intrinsic factor produces a substance necessary for the normal development of red blood cells. The product formed is absorbed from the intestine, stored in the liver and released to the body tissues for utilization as needed. Macrocytic anemia will be produced if there is a disturbance of any of the factors which are involved in this mechanism.

The value of food as a satisfactory source of the extrinsic factor for the treatment of macrocytic anemia due to deficiency has been demonstrated clinically<sup>53</sup> and experimentally<sup>54</sup>. Although the stomach

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51 Stare, F. J., and Thompson, L. D. Hepatoflavin and Pernicious Anemia, *Proc Soc Exper Biol & Med* **33** 64, 1935.

52 Sturgis, C. C., Isaacs, Raphael, Goldhamer, S. M., Bethell, F. H., and Farrar, G. E., Jr. Blood, *Arch Int Med* **55** 1001 (June) 1935. Vaughan, J. M. Anaemias Due to a Deficiency of the Principle in Liver Which Is Effective in the Treatment of Addisonian Pernicious Anemia, *Proc Roy Soc Med* **28** 475, 1935. Castle<sup>1</sup>.

53 (a) Castle, W. B., Rhoads, C. P., Lawson, H. A., and Payne, G. C. Etiology and Treatment of Sprue. Observations on Patients in Puerto Rico and

tissue is the source of the intrinsic factor, gastrectomy usually results in microcytic rather than macrocytic anemia<sup>55</sup> The same results have been observed by other investigators<sup>56</sup> Apparently other nutritional factors, such as minerals and vitamins, and their effects on the body tissues are important in the production of secondary anemia The microcytic anemia produced in animals is also explained by the fact that there is a constitutional difference between man and animals It has been demonstrated that desiccated dog stomach is inactive or less than one-half as potent as hog stomach and that dog liver is less effective than calf liver<sup>56a</sup>

Obstruction of the small intestine,<sup>57</sup> infestation with a tapeworm,<sup>58</sup> celiac disease, gastrocolic fistula and sprue<sup>53</sup> have all been observed in association with macrocytic anemia Study of the bone marrow in some cases of sprue, during relapse and during remission, revealed a striking similarity to the pathologic changes observed in pernicious anemia<sup>53a</sup>

It has recently been demonstrated that experimental cirrhosis is associated with macrocytic anemia<sup>59</sup> These observations tend to confirm the clinical reports of macrocytic anemia occurring in hepatic disease<sup>60</sup> There appears to be sufficient evidence that the intrinsic

Subsequent Experiments on Animals, Arch Int Med **56** 627 (Oct) 1935 (b) Snell, A M, Camp, J D, and Watkins, C H Nontropical Sprue (Chronic Idiopathic Steatorrhea), Proc Staff Meet, Mayo Clin **10** 177, 1935 (c) Fairley, N H Tropical Sprue and Its Modern Treatment, Brit M J **2** 1192, 1934

54 Day, P L, Langston, W C, and Shukers, C F Leukopenia and Anemia in Monkey Resulting from Vitamin Deficiency, J Nutrition **9** 637, 1935 Miller and Rhoads<sup>3</sup>

55 Hartman, H R, and Eusterman, G B Anemia Following Operations on the Stomach, Am J Digest Dis & Nutrition **1** 829, 1935 Hunter, D New Aspects of Deficiencies in Nutrition, Lancet **1** 1025, 1935 Hartfall, S J Gastrectomy and Gastro-Enterostomy Anemia, Guy's Hosp Rep **84** 448, 1934 Miller and Rhoads<sup>3</sup>

56 (a) Ivy, A C, Richter, O, Meyer, A F, and Greengard, H The Relation of Gastrectomy to Anemia on the Presence of the Substances Effective in Pernicious Anemia in Canine Stomach and Liver, Am J Digest Dis & Nutrition **1** 116, 1934 (b) Dragstedt, C A, Bradley, J D, and Mead, F B Effect of Iron on Hemoglobin Regeneration in Gastrectomized Dogs, Proc Soc Exper Biol & Med **33** 58, 1935

57 Jonsson, E Des anemies qui, dans la tuberculose, rappellent l'anémie pernicieuse, Acta med Scandinav **83** 505, 1934

58 Hunnicutt, T N, Jr An Anemia Associated with a Fish Tapeworm (Diphyllobothrium Latum) Infestation, J A M A **104** 1984 (June 1) 1935

59 Higgins, G M, and Stasney, J Macrocytic Anemia in Experimental Cirrhosis, Proc Staff Meet, Mayo Clin **10** 429, 1935

60 Malamos, B Das rote Blutbild bei Lebererkrankungen, Deutsches Arch f klin Med **177** 209, 1935 Wilkinson, J F, and Israels, M C G Achresthic Anaemia, Brit M J **1** 139 and 194, 1935 Kersley, G D Atypical Megalocytic Anaemia, ibid **2** 994, 1935

factor may be present in the stomach, but because of damage to the liver the hematopoietic substance cannot be stored and presented to the bone marrow for utilization, and as a result macrocytic anemia develops

In addition to the foregoing factors concerned in the production of macrocytic anemia, other causes have been suggested<sup>61</sup>

Treatment of the anemia associated with these various conditions depends on which factor or factors are contributing to the cause in each given instance. If the intrinsic or the extrinsic factor is absent, liver administered orally may be appropriate, however, if there is a disturbance of absorption or storage, the administration of liver parenterally should be instituted. A well balanced diet has also been recommended.

#### ANEMIA OF PREGNANCY

It is customary to classify in two types anemia directly attributable to the gravid state. The more prevalent is the hypochromic and microcytic anemia so often associated with a deficiency of iron. Of 51 pregnant women studied by Davies and Shelley,<sup>62</sup> 6 were found to have anemia of the hypochromic type. Achlorhydria or hypochlorhydria was found in all but 1 of the women. Schultz<sup>63</sup> emphasized that in anemia of pregnancy of the hypochromic type there are evidences of active regeneration of the blood, the condition tends to improve spontaneously after childbirth, and an especially important rôle in its production is the loss of blood whether by previous menorrhagia, abortion or childbirth. He found that after repeated pregnancies spontaneous recovery from this type of anemia is greatly prolonged. Simple iron preparations are effective against the hypochromic anemia of pregnancy, but the response to treatment is slower than in nonpregnant persons.<sup>64</sup>

Macrocytosis and hyperchromia characterize the second and much less common type of anemia of pregnancy. In addition to dietary deficiencies and defects of gastric secretion as causative factors in the development of anemia of the macrocytic or pernicious type, Wintrobe and Shumacker<sup>26</sup> suggested that the demands of fetal hematopoiesis may place an excessive drain on the maternal supply of the hepatic

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61 Stern, R. O. Achlorhydria in the Psychoses, with Special Reference to Coincident Anaemia, *J Ment Sc* **81** 358, 1935. McGowan, J. P. Pernicious Anaemia. Some Considerations in Regard to Its Nature and Pathogenesis, *Edinburgh M J* **42** 293, 1935. Keyes, H. R. The Mycology of Sprue and Pernicious Anemia, *Am Med* **41** 9, 1935. Jonsson<sup>57</sup>

62 Davies, D. T., and Shelley, U. Some Observations on Hypochromic Anaemia and Its Relation to Pregnancy, *Lancet* **2** 1094, 1934.

63 Schultz, W. Die essentielle hypochrome Anämie mit Berücksichtigung der essentiellen Schwangerschaftsanämie, *Verhandl d deutsch Gesellsch f inn Med* **47** 327, 1935.

64 Bethell, F. H. The Application of Diagnostic Criteria to the Treatment of the Anemias, *New York State J Med* **35** 799, 1935.

principle essential for normal maturation of the erythrocytes Strauss<sup>65</sup> found that adequate treatment of pernicious anemia of pregnancy requires the use of much larger doses of liver extract orally or parenterally than are needed in the management of the usual Addisonian pernicious anemia Ionesco and Bonciu<sup>66</sup> have obtained good results in the treatment of this form of anemia by the use of preliminary transfusions of blood followed by the administration of 250 Gm of fresh cooked liver daily

## ANEMIA ASSOCIATED WITH OTHER DISEASE ENTITIES

### HEMOLYTIC JAUNDICE

The behavior of the red blood cells after splenectomy was studied by Levi and Bairati<sup>67</sup> The microcytosis tended to be replaced by a normocytosis, with a decrease in the number of reticulocytes, although some microcytes persisted and the resistance of the red blood cells to hypotonic solutions of sodium sulfate continued to be abnormal The authors expressed the belief that the spheroidal microcytosis does not represent a constitutional defect of erythropoiesis but is secondary to hyperhemolysis

In a study of bone marrow, Dameshek<sup>68</sup> found in 1 case that the ratio of red blood cells to white blood cells was 0.4:1, and the percentage of erythroblasts was 80 per cent, in another case the red blood cell-white blood cell ratio was 1:1, with an increase in the erythroblasts to 80 per cent There was a definite increase in the number of histiocytes

In a case described by Waugh,<sup>69</sup> marked improvement followed the use of liver extract intravenously Smith<sup>70</sup> was able to trace the disease through four generations in a patient under his care In Langston's<sup>71</sup>

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65 Strauss, M. B. The Etiology and Prevention of Anemia in Pregnancy, *Ann Int Med* **9** 38, 1935

66 Ionesco, V. T., and Bonciu, D. Contribution a l'étude de l'anémie pernicieuse gravidique, *Sang* **9** 510, 1935

67 Levi, G. M., and Bairati, A. Distribution of Erythrocyte Population in Regard to Diameters and Osmotic Resistance in Splenectomized Cases of Hemolytic Icterus. Contribution to Understanding of Pathogenesis of Disease, *Am J M Sc* **190** 610, 1935

68 Dameshek, W. Biopsy of the Sternal Bone Marrow. Its Value in the Study of Diseases of Blood-Forming Organs, *Am J M Sc* **190** 617, 1935

69 Waugh, T. R. Pernicious Anemia in an Individual with Familial Hemolytic Jaundice, *Folia haemat* **53** 291, 1935

70 Smith, G. O. Chronic Hereditary Hemolytic Jaundice, *J A M A* **105** 1187 (Oct 12) 1935

71 Langston, W. Hemolytic Icterus with Infantilism, *South M J* **28** 316 1935

case hemolytic icterus was associated with infantilism. Splenectomy and hormone therapy were followed by a return to normal.

Doan, Curtis and Wiseman<sup>72</sup> noted an increase in the red blood cell count of a million or more immediately after splenectomy. Several factors appeared to play a part: disgorgement of the sequestered blood cells from the splenic reservoir and sudden elimination of the destructive activity of the splenic phagocytes and hyperactive hematopoiesis. The spleen is considered as the major pathologic agent in congenital hemolytic jaundice. Splenectomy is indicated as a prophylactic measure against clinical exacerbations of excessive hemolytic activity in the chronic and subacute manifestations of the disease as well as in acute hemoclastic crises, whether spontaneous or precipitated, and regardless of the severity of the anemia.

Heilmeyer<sup>73</sup> described hemolytic hypersplenism as a definite form of acquired hemolytic jaundice. In this condition there is a severe degree of hemolytic anemia, with reticulocytosis, microspherocytosis and splenic tumor. The condition is of sudden onset, there is no history of the disease in the family, and cure occurs after splenectomy. The author measured the red blood cells from the splenic artery and vein and found an increase in microspherocytosis in the latter. Severe infections and endocrine dyscrasias may be etiologic factors.

In hemolytic jaundice the plasma phosphatase is normal in amount, whereas in jaundice due to mechanical obstruction of the bile ducts the amount is increased. In toxic or infective disease of the liver the amount may be normal or elevated (Herbert<sup>74</sup>).

Daland and Worthley<sup>75</sup> studied the resistance of red blood cells to hemolysis in solutions of sodium chloride in a number of diseases. After splenectomy in hemolytic jaundice a temporary hypochromic blood picture may be accompanied by increased maximal resistance. Before splenectomy, decreased maximum resistance is the rule. Decreased minimal resistance is common in this disease, rarely is it normal.

Rozendaal, Comfort and Snell<sup>76</sup> concluded that an indirect van den Bergh reaction in serum containing bilirubin in amounts more than

72 Doan, C. A., Curtis, G. M., and Wiseman, B. K. Hemolytotoxic Equilibrium and Emergency Splenectomy, *J. A. M. A.* **105** 1567 (Nov. 16) 1935.

73 Heilmeyer, L. Hamolytische Hypersplenie. Erworbenener hamolytischer Ikterus, *Deutsches Arch. f. klin. Med.* **178** 89, 1935.

74 Herbert, Freda K. Plasma Phosphatase in Various Types of Jaundice, *Brit. J. Exper. Path.* **16** 365, 1935.

75 Daland, G. A., and Worthley, K. Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride. *Observations in Blood Disorders*, *J. Lab. & Clin. Med.* **20** 1122, 1935.

76 Rozendaal, H. M., Comfort, M. W., and Snell, A. M. Slight and Latent Jaundice. The Significance of Elevated Concentrations of Bilirubin Giving an Indirect van den Bergh Reaction, *J. A. M. A.* **104** 374 (Feb. 2) 1935.

normal does not always mean hemolytic disease. In hemolytic anemia associated hepatic injury is almost universal.

Watson<sup>77</sup> isolated a new porphyrin from the feces of a patient during a hemolytic crisis. It occurred in association with a marked increase in coproporphyrin I.

For the congenital as opposed to the acquired (chemical or bacterial toxin) type of hemolytic jaundice, Lehdorff<sup>78</sup> based the diagnosis on icterus, pallor, splenomegaly, with microcytosis, reduced resistance of the red blood cells to hypotonic solutions of sodium chloride and increase in the number of reticulocytes. In children the icterus may be mild or absent, and pallor is not constant. The microcytosis is characteristic, the average corpuscular diameter being 5.8 microns instead of 7.8. The cells are spheroid rather than flat, and the average volume is greater than normal (100 cubic microns). The hemoglobin content of the red blood cell is relatively high, with a color index of 1 or above. The author considered that the anemia results from the attempt of the reticulo-endothelial system, especially the spleen, to remove the abnormally shaped (spheroid) red blood cells. Splenomegaly develops, and later icterus, if the liver cannot metabolize the excess pigment adequately. Transfusion of blood is recommended during the acute attack and occasionally treatment with liver and iron preparations. Splenectomy should be done only when the hemolytic crises are recurrent, but during the periods of remission no therapy is indicated.

#### APLASTIC ANEMIA

The literature contains reports of cases of aplastic types of anemia in association with abdominal lymphogranuloma, ankylostomiasis and arsphenamine, neoarsphenamine (Imrie<sup>79</sup>), benzene (Cabot,<sup>80</sup> case 21301) and acetarsone poisoning and also during the course of the treatment of tuberculosis with gold compounds (de Lavergne and Bichat<sup>81</sup>), and after radiotherapy (Marchal, Mallet, Soulié and Grupper<sup>82</sup>). There

77 Watson, C. J. Concerning Naturally Occurring Porphyrins. Isolation of Hitherto Undescribed Porphyrin Occurring with Increased Amount of Coproporphyrin I in Feces of Case of Familial Hemolytic Jaundice, *J. Clin. Investigation* **14** 110, 1935.

78 Lehdorff, H. Hamolytische Anämie—Die Kugelzellenkrankheit, *Med. Klin.* **31** 74, 1935.

79 Imrie, A. H. Aplastic Anaemia Following Neokharsivan, *Lancet* **2** 73, 1935.

80 Aplastic Anemia (Benzol Poisoning), Cabot Case 21301, *New England J. Med.* **213** 182, 1935.

81 de Lavergne, V., and Bichat, J. L'aleucie hemorrhagique accident de la chrysothérapie, *Rev. med. de l'est* **63** 457, 1935.

82 Marchal, G., Mallet, L., Soulié, P., and Grupper, C. Deux cas d'aleucie hemorrhagique post-radiothérapique, *Sang* **9** 766, 1935.

is considerable confusion in the literature concerning the use of the term aplastic anemia, some authors referring to a selective decrease in the number of red blood cells and others to a panmyelophthisis, whereas in several cases reference is made to aplastic anemia during the course of aleukemic leukemia. The treatment appears to be limited to the transfusion of blood. The administration of pentose nucleotide is not effective (Holmes <sup>83</sup>)

#### CANCER

\* The blood picture associated with cancer is neither pathognomonic nor constant, nor does the anemia associated with cancer give any indication of the site of the malignant process. The anemia may be macrocytic or microcytic, and the color index, high or low. Usually there is leukocytosis. The number of platelets in the blood may be increased, decreased or normal. The etiology of the anemia has been discussed by many investigators,<sup>84</sup> who have offered several explanations. If there is a disturbance in iron metabolism (failure of absorption or chronic hemorrhage), microcytic anemia results. Secondary anemia is also attributed to a toxic effect on the bone marrow or to hemolysis. Macrocytic anemia associated with cancer of the stomach may result from an insufficiency or lack of secretion of the "active" principle by the cancerous gastric mucosa,<sup>85</sup> from metastasis to the bone marrow or from the coincidental existence of pernicious anemia and cancer. In view of the relationship of macrocytic anemia and cancer of the stomach, it has been suggested that routine roentgenograms of the gastro-intestinal tract be made.<sup>84d</sup> The treatment of the anemia depends on the etiology, and though it may be aided by proper diet, large doses of iron and antianemic therapy, it cannot be eliminated without removal of the primary causal factor.

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83 Holmes, J. M. Aplastic Anemia. Two Fatal Cases Treated by Blood Transfusion and Pentose Nucleotide, *Lancet* **2** 71, 1935

84 (a) Labbe, M., and Balmus. Anémie pernicieuse et cancer de l'estomac, *Sang* **9** 113, 1935. (b) Miller, T. G. Addisonian Anemia and Carcinoma of the Stomach in the Same Individual. Report of Three Cases, Chronic Gastritis as Probable Basis for Both Diseases, *Internat Clin* **1** 167, 1935. (c) Weil, P. E., and Bernard, J. Le cancer de l'estomac chez les hémérétiques guéris, *Presse méd* **43** 97, 1935. (d) Heath, C. W. Treatment of Anemia in Inoperable Carcinoma of Stomach, *M. Clin North America* **18** 1183, 1935. (e) Priestley, J. T., and Heck, F. J. Bleeding Malignant Polypoid Lesions in the Cardia of the Stomach Associated with Severe Anemia. Report of Three Cases, *Ann Surg* **101** 839, 1935.

85 Goldhamer, S. M. Unpublished data

## INFECTION

A disturbance in the balance between the production and the destruction of the red blood cells may be caused by infection. Usually secondary anemia results. The response of the leukopoietic tissue to infection depends on the state of the bone marrow and on the type of infection.<sup>86</sup> The total white blood cell count may be used as an index of the degree of response of the bone marrow, the maturity or immaturity of the leukocytes as a measure of the effort of response of the leukopoietic tissue and the number of polymorphonuclear neutrophils with cytoplasmic changes as an index of the severity of the infection. In following the course of an infection it appears that more information can be obtained by determining such changes in the cytoplasm of the white blood cells as vacuolation, toxic granulation and the presence of a bluish or grayish color of the cytoplasm than by noting the number of lobes or filaments of the nuclei.<sup>87</sup>

## ENDOCRINE DISTURBANCES

Clinically it has been observed by some authors that specific changes in the blood are associated with hyperthyroidism, however, there appears to be a wide divergence of opinion concerning this fact. The anemia often noted in association with myxedema may be macrocytic or microcytic and may be directly related to the dysfunction of the thyroid gland or may exist as an independent condition. The possibility that macrocytic anemia is caused by a decrease in gastric function was investigated, and it was noted that in patients with endocrine dysfunction gastric secretion may be normal or reduced.<sup>15</sup> Anemia has also been reported in association with the syndrome of menstrual disorder and low metabolic rate without myxedema.<sup>88</sup> Marked improvement in this type of anemia was obtained with thyroid medication and also with large doses of iron.<sup>89</sup>

Experimentally<sup>90</sup> it was demonstrated that intravenous or intramuscular injections of an extract prepared from the posterior lobe of

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86 Bethell, F. H. The Response to Infection in Bone Marrow Dyscrasias, *J. Lab. & Clin. Med.* **20** 362, 1935.

87 Meranze, D. R., Mendell, T. H., and Meranze, T. Cytoplasmic Changes in the Peripheral Neutrophil as an Aid in Diagnosis and Prognosis, *Am. J. M. Sc.* **189** 639, 1935. Haden, R. L. Qualitative Changes in Neutrophilic Leukocytes, *Am. J. Clin. Path.* **5** 354, 1935. Bethell<sup>86</sup>

88 Haines, S. F., and Mussey, R. D. Certain Menstrual Disturbances Associated with Low Basal Metabolic Rates Without Myxedema, *J. A. M. A.* **105** 557 (Aug. 24) 1935.

89 Unpublished data, Simpson Memorial Institute.

90 Dodds, E. C., and Noble, R. L. Relation of the Posterior Lobe of the Pituitary Gland to Anaemia and to Blood Formation, *Nature*, London **135** 788, 1935. Dodds, E. C., Hills, G. M., Noble, R. L., and Williams, P. C. The Posterior Lobe of the Pituitary Gland Its Relationship to the Stomach and to the Blood Picture, *Lancet* **1** 1099, 1935.



the pituitary gland caused hemorrhage in the acid-bearing area of the stomach, severe macrocytic anemia, reticulocytosis, hyperplasia of the bone marrow, leukocytosis and an increase in the production of bile. The authors hypothesized that the pituitary gland may control hematopoiesis by its effect on the stomach and reticulo-endothelial system, and this may account for the changes in the blood seen in association with disorders of the pituitary gland.

After adrenalectomy in rats<sup>91</sup> the peripheral blood showed an increase in the number of platelets and leukocytes, a slight increase in the number of lymphocytes and a slight reduction in the number of polymorphonuclear leukocytes. The injection of an extract of the adrenal cortex into normal rabbits did not alter the number of leukocytes.<sup>92</sup> In view of the stimulating effect of epinephrine on the leukopoietic system, a simple test was devised for clinical purposes to distinguish catarrhal from other forms of jaundice.<sup>93</sup> Usually leukopenia is present in cases of catarrhal jaundice. Whereas the injection of 1 cc of a 1:1,000 solution of epinephrine produced an increase of from 50 to 300 per cent in the number of white blood cells, in cases of catarrhal jaundice there is often no increase and never more than a 40 per cent rise in the total number of leukocytes.

#### IRON DEFICIENCY ANEMIA

The value of iron as a specific remedy for a frequent type of anemia has continued to receive recognition. Davidson, Fullerton and Campbell,<sup>94</sup> after adopting standards for normal values for hemoglobin and erythrocytes at the various age groups in both sexes, examined 3,500 persons, representing a cross-section of the poor of Aberdeen. They found anemia to be relatively infrequent, except in infants between the eleventh and the twenty-third month of life and in adult women. Abnormally low values were found in 41 per cent of infants under 2 years of age, 32 per cent of children of preschool age, 16 per cent of adolescent women and 45 per cent of adult women. The incidence

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91 Sheket, H. A., Friedman, D. L., and Nice, L. B. Number of Thrombocytes and Leucocytes in Blood and Adrenalectomized Rats, *Proc Soc Exper Biol & Med* **32** 608, 1935.

92 Fox, C. A., and Whitehead, R. W. Effect of Cortico-Adrenal Extract on Leukocytes in Blood of Normal Adult Rabbits, *Proc Soc Exper Biol & Med* **32** 756, 1935.

93 Weiner, J. G. The Adrenalin-Leucocyte Count in Catarrhal Jaundice, *M Rec* **141** 453, 1935.

94 Davidson, L. S. P., Fullerton, H. W., and Campbell, R. M. Nutritional Iron Deficiency Anemia with Special Reference to Prevalence and Age and Sex Incidence, *Brit M J* **2** 195, 1935.

of anemia was greatest among women of the reproductive age who had borne children, it became progressively less after the menopause. Anemia was not found in adolescent and adult males, except in association with organic disease.

The prevalence of anemia in early childhood has been generally attributed to the low iron content of the usual infant diet coupled with the demand occasioned by rapid growth. These, undoubtedly, are important factors, but, as in the case of adults, diminished gastric secretion of hydrochloric acid may play an important rôle in causing nutritional anemia. Following an earlier report of Hawksley, Lightwood and Bailey, Ogilvie<sup>14</sup> found that of 13 young children with achlorhydria or hypochlorhydria 11 suffered from anemia of the iron deficiency type. On the other hand, of 18 patients with anemia of this type 10 secreted acid in normal quantities. They concluded that a diet poor in iron may be a sufficient single cause for nutritional anemia in children but that, furthermore, in spite of an ordinarily adequate supply of iron-containing food, anemia may develop as the result of gastric secretory defect. A similar study made by Faber, Mermod, Gleason and Watkins<sup>95</sup> led them to the supposition that the physiologic hypochlorhydria present in the first two years of life may cause poor absorption of iron-containing food, resulting in inadequate production of hemoglobin. In a discussion of anemia in children, Parsons and Smallwood<sup>96</sup> attributed nutritional anemia in the great majority of cases to a lack of iron. They recommended the use of 0.2 Gm of reduced iron daily or 1 Gm of ferrous sulfate daily. In some cases it is advisable, according to these authors, to supplement iron medication with yeast. The value of copper in the treatment of nutritional anemia in children has not been conclusively established, although recently its use has been advocated by Elvehjem, Siemers and Mendenhall<sup>97</sup>. They studied children with a hemoglobin content ranging from 9 to 11 Gm per hundred cubic centimeters of blood. These values were raised to from 12 to 13.5 Gm. They found a combination of ferric pyrophosphate and cupric sulfate, yielding 25 mg of metallic iron and 1 mg of metallic copper daily to be particularly efficacious. The response to iron alone was found to be slower than when copper was used. They stated that the use of large doses

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95 Faber, H. K., Mermod, C., Gleason, A. L., and Watkins, R. P. Microcytic, Hypochromic (Iron-Deficiency) Anemia in Infancy and Childhood. Its Relation to Gastric Anacidity and to Simple Achlorhydric Anemia of Adults, *J. Pediat.* **7** 435, 1935.

96 Parsons, L. G., and Smallwood, W. C. The Anaemias of Infancy and Childhood, *Practitioner* **134** 298, 1935.

97 Elvehjem, C. A., Siemers, A., and Mendenhall, D. R. Effect of Iron and Copper Therapy on Hemoglobin Content of the Blood of Infants, *Am. J. Dis. Child.* **50** 28 (July) 1935.

of iron is undesirable because of its interference with the assimilation of phosphorus. On the other hand, the studies of Sachs, Levine and Fabian<sup>98</sup> indicate that an inverse relationship of the iron and copper content of the blood may exist in persons with hypochromic anemia. They found no evidence of a depletion of copper.

Idiopathic hypochromic anemia, as a distinct clinical entity, has, during the past year, received less attention than formerly. It is now generally grouped with the hypochromic and microcytic anemias prevalent in middle-aged women, which are due to a variety of factors, including dietary defect, lack of hydrochloric acid in the stomach, menorrhagia and repeated pregnancy. In a discussion of this condition Schulten<sup>99</sup> emphasized the value of large doses of iron and pointed out the relatively greater efficacy of the ferrous salts over the elemental and ferric forms of the metal. He advocated the use of 10 Gm of reduced iron daily or from 0.5 to 1 Gm of ferrous chloride daily. Such an amount of reduced iron is undoubtedly excessive, since it has been shown that 1.5 Gm of reduced iron, even in the presence of achlorhydria, will cause an average gain in hemoglobin of 153 mg per hundred cubic centimeters, or approximately 1 per cent, daily.<sup>64</sup> Moreover, the ingestion of large amounts of metallic iron is undesirable from a mechanical point of view alone, since Sjöberg<sup>100</sup> has demonstrated that it may result in intestinal obstruction.

Dysphagia complicating hypochromic anemia, known as the Plummer-Vinson syndrome, is often attributable to a mechanical obstruction of the upper portion of the esophagus, according to Hoover.<sup>101</sup> He advised dilatation of the esophagus together with iron medication for the relief of this condition. However, it has been the experience of most observers that the dysphagia will be relieved on improvement of the anemia.

The rôle of the stomach in the assimilation of iron has received additional emphasis from the investigations of Fasiani and Chiatellino.<sup>102</sup> They reported the results of studies of the blood of a large group of patients treated by operation for gastroduodenal ulcer. In many persons, especially in women, partial gastric resection led after a number of years to hypochromic anemia with all the characteristics of idiopathic hypo-

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98 Sachs, A., Levine, V. E., and Fabian, A. A. Copper and Iron in Human Blood, *Arch Int Med* **55** 227 (Feb.) 1935.

99 Schulten, H. Zur Klinik der essentiellen hypochromen Anämie, *München med Wchnschr* **82** 697, 1935.

100 Sjöberg, H. Symptoms of Ileus from Retention of Iron in Cecum Following Administration of Large Doses of Iron, *Acta med Scandinav* **85** 129, 1935.

101 Hoover, W. B. The Syndrome of Anemia, Glossitis, and Dysphagia. Report of Cases, *New England J Med* **213** 394, 1935.

102 Fasiani, G. M., and Chiatellino, A. Syndromes anémiques chez les opérés de l'estomac, *Presse med* **42** 2080, 1934.

chronic anemia, including achlorhydria, and often to changes in the tongue and nails. The anemia occurred most frequently after a Billroth (no 2) or a Polya operation, which involves more extensive removal of the stomach.

Although the classification of anemia on the basis of the size and hemoglobin content of the red blood cells offers definite advantages and has recently been reemphasized by Haden,<sup>103</sup> it is unjustifiable to use such a classification as an exclusive therapeutic guide. Hypochromia and microcytosis reflect the status of the blood-forming organs rather than denote the lack of a single substance required for hematopoiesis. The possible influence of dietary deficiencies other than deficiency of iron in causing anemia or in retarding regeneration of the blood has been emphasized by Sturgis and Farrar,<sup>104</sup> by Baker<sup>105</sup> and particularly by Minot.<sup>106</sup> Minot has also suggested that iron may be of benefit other than as simply supplying a deficiency. In this connection it is of interest that a group of French investigators<sup>107</sup> have reported benefit from the use of iron in the treatment of patients suffering with lassitude, digestive disorders and glossitis, even though such patients had no anemia. They have observed, after iron medication, restoration of the papillae of the tongue and, in 1 case in which gastroscopy was done before and after treatment, correction of atrophy of the gastric mucosa.

## DEFINITE DISEASE ENTITIES OF THE BLOOD

### POLYCYTHEMIA

Headache, dizziness and paresthesia may be the presenting symptoms of polycythemia (Adams<sup>108</sup>). Splenomegaly is always associated with this condition, and hepatomegaly is frequently present. There is a tendency to bleed easily. In Adams' series, every patient subjected to a surgical procedure suffered from postoperative hemorrhage. For

103 Haden, R. L. Hypochromic Anemia, *Ohio State M J* **31** 583, 1935

104 Sturgis, C. C., and Farrar, G. E. Hemoglobin Regeneration in the Chronic Hemorrhagic Anemia of Dogs (Whipple). The Effect of Iron and Protein Feeding, *J Exper Med* **62** 457, 1935

105 Baker, J. P., Jr. Anemias Dependent upon Food Deficiencies, *Virginia M Monthly* **62** 335, 1935

106 Minot, G. R. The Anemias of Nutritional Deficiency. Etiology, Diagnosis, Treatment and Prevention, *J A M A* **105** 1176 (Oct 12) 1935

107 (a) Chevallier, P., Moutier, F., Stewart, W., Sevaux, A., and Ely, Z. L'atrophie gastrique et la therapeutique antianémique dans des affections sans anémie. Conception d'une maladie à manifestations diverses dont les anémies essentielles ne sont que des formes cliniques graves, *Bull et mem Soc med d hôp de Paris* **50** 1606, 1934. (b) Chevallier, P., Moutier, F., and Ely, Z. Un cas de chlorose fruste de la puberté avec atrophie gastrique cliniquement latente, *Sang* **9** 748, 1935

108 Adams, L. J. Polycythemia Vera, with Special Reference to Nervous Manifestations. Analysis of Nine Cases, *Canad M A J* **32** 128, 1935

treatment, Adams used phenylhydrazine hydrochloride and roentgen irradiation over the long bones in small repeated doses. Langer,<sup>109</sup> postulating that polycythemia is due to an imbalance of the vegetative nervous system, irradiated the paravertebral ganglions (vertebral column). There was a decrease in the red cell blood count during the months following cessation of the roentgen treatment. Nisbet<sup>110</sup> also advocated roentgen therapy for this condition.

Weber<sup>111</sup> described a patient who had erythremia, migraine, gout and thrombophilia. At one time the symptoms, together with tarry stools, suggested duodenal ulcer, but no bleeding points were discovered at autopsy. There was a tendency to thrombus formation, and this accounted for many of the symptoms. Wilbur and Ochsner<sup>112</sup> found 12 instances of peptic ulcer (10 of duodenal and 2 of gastric) in 143 patients with polycythemia, as compared with from 2 to 32 per cent in a control group.

Lunedei and Liesch<sup>113</sup> attributed polycythemia and gastroduodenal ulcer to diencephalic hypofunction. They noted gastroduodenal ulcer, essential polycythemia and Froehlich's syndrome in various members of the same family. Singer<sup>114</sup> noted the disappearance of polycythemia after gastric resection in a patient in whom the disease was associated with peptic ulcer.

As to the etiology, Beyne, Binet and Strumza<sup>115</sup> stated that anoxemia is the primary feature and that polycythemia is of respiratory origin. Reznikoff, Foot and Bethea<sup>116</sup> noted distinct capillary thickening.

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109 Langer, H. Roentgen Therapy in Hyperplastic Blood Dyscrasias. New Technique for Myeloid and Lymphatic Leukemia, Polycythemia Rubra Vera and Hodgkin's Disease, *Am J Roentgenol* **34** 214, 1935.

110 Nisbet, A. T. Treatment of Blood Dyscrasias by X-Radiation, *J Cancer Research Com, Univ Sydney* **6** 201, 1935.

111 Weber, F. P. Erythraemie mit Migrane, Gicht und Thrombophilie, *Klin Wchnschr* **14** 15, 1935.

112 Wilbur, D. L., and Ochsner, H. C. Association of Polycythemia Vera and Peptic Ulcer, *Ann Int Med* **8** 1667, 1935.

113 Lunedei, A., and Liesch, E. Ulcera gastro-duodenale policitemia essenziale, sindrome adiposo-genitale di Froehlich in vari membri di una stessa famiglia. Considerazione sull' importanza delle disfunzioni diencefaliche nella patogenesi dell' ulcera gastro-duodenale e della poliglobulia e sui rapporti fra queste, *Riv di clin med* **36** 485, 1935.

114 Singer, Karl. Gibt es eine gastrogene Polyglobulie? *Klin Wchnschr* **14** 751, 1935.

115 Beyne, J., Binet, L., and Strumza, M. V. Sur le mecanisme de la polyglobulie d'origine respiratoire, *Compt rend Soc de biol* **118** 1177, 1935.

116 Reznikoff, P., Foot, N. C., and Bethea, J. M. Etiologic and Pathologic Factors in Polycythemia Vera, *Am J M Sc* **189** 753 1935.

ing, probably fibrosis, in the bone marrow of 7 patients with polycythemia and 6 showed, in addition, marked subintimal and adventitial fibrosis of the subarteriolar capillaries, arterioles and arteries. Slight thickening of the capillaries was seen in the agranulocytic bone marrows of 3 of 5 patients. In cases of general arteriosclerosis medial fibrosis was also evident. The authors concluded that "the vascular changes, especially in the capillaries of the bone marrow in polycythemia vera patients, suggest the possibility that these lesions may result in anoxemia of the bone marrow with compensatory or excess compensatory polycythemia."

Sgalitzer<sup>117</sup> treated patients with polycythemia with "total irradiation." He gave treatments of twenty minutes each to the whole body (except the eyes and genitalia), applying about 25 roentgens to the surface of the body. These were given for six successive days, with weekly intervals between courses. Treatment was discontinued before the leukocyte count fell to below 3,000 per cubic millimeter. There was symptomatic improvement, with relapse in from eighteen months to five years. In the patient treated by Bishop, Bishop and Trubeck,<sup>118</sup> roentgen irradiation of the long bones and spleen appeared to be associated with a gradual increase in the red blood cell count rather than a reduction, although there was subjective improvement.

Reimann and Breuer<sup>119</sup> advocated venesection, with removal of from 300 to 400 cc of blood, twice weekly until the hemoglobin content has fallen to from 80 to 90 per cent. They reported excellent remissions with the effects persisting for approximately two years. The treatment aims to deplete the body of stores of blood-forming materials.

In a case of nonfamilial erythremia, Briggs and Oerting<sup>16</sup> produced a remission with gastric lavage from four to six times daily. In cases of familial erythremia this procedure relieved the symptoms and prevented an increase in the red blood cell count.

Tyler and Baldwin<sup>120</sup> produced polycythemia in rats by exposing them to atmospheres low in oxygen for from two to fifteen days. After normal pressure was again used, 50 per cent of the excess erythrocytes disappeared within six hours. Possible explanations were (1) the absorption of the blood by some organ, (2) dilution of plasma and (3) restoration to normal after a period of anhydremia.

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117 Sgalitzer, M. Röntgentotalbestrahlung bei Polycythämie, *Wien klin Wchnschr* **48** 675, 1935.

118 Bishop, L. F., Bishop, L. F., Jr., and Trubeck, M. Erythremia, *Ann Int Med* **8** 1602, 1935.

119 Reimann, F., and Breuer, A. Die Aderlassbehandlung der Erythraemie, Eine therapeutische Untersuchung, *Ztschr f klin Med* **128** 238, 1935.

120 Tyler, D. B., and Baldwin, F. M. Rate of Disappearance of Red Cells in Polycythemic Rats, *Proc Soc Exper Biol & Med* **33** 165, 1935.

## ABNORMALITIES OF BLOOD CLOTTING

Several interesting experiments relating to coagulation of the blood have been performed *in vitro*<sup>121</sup> As a result of these observations Eagle concluded that thrombin is the cause of coagulation and is an enzyme, that prothrombin is the precursor of thrombin, that the blood platelets accelerate the rate of the formation of thrombin, although their mode of action is not known, and that there is no evidence of species-specific activity of platelets in the transformation of thrombin It was also demonstrated that all the elements of hemophilic blood which partake in coagulation are normal and that the deficiency of the clotting mechanism in hemophilic blood is probably the result of the slow formation of thrombin<sup>122</sup> A most comprehensive review by Howell concerning the theories of blood coagulation has recently been published<sup>123</sup>

Since the chemical nature of the various elements which are involved in blood clotting are known, it has been recommended that diets high in protein and fat be given to persons in whom there is a deficiency of the blood-clotting mechanism<sup>124</sup>

## PURPURA HAEMORRHAGICA

Many etiologic factors may cause purpura, and various forms have been classified The clinical value of these complex classifications is somewhat doubtful The degree of bleeding is determined by three factors (*a*) the platelets, (*b*) the permeability of the capillaries and (*c*) the plasma The diminution in the number of platelets may be due to a deficient formation in the bone marrow<sup>125</sup> or to increased destruction by the reticulo-endothelial system (primarily the spleen) The disturbance of formation of the platelets in the bone marrow has been ascribed to a hormonal deficiency, resulting in the failure of the megakaryoblasts to mature The decrease in the number of platelets is thought by some to be the result of hemorrhage rather than the

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121 Eagle, H Studies on Blood Coagulation The Rôle of Prothrombin and of Platelets in the Formation of Thrombin, *J Gen Physiol* **18** 531, 1935, Studies on Blood Coagulation The Formation of Fibrin from Thrombin and Fibrinogen, *ibid* **18** 547, 1935

122 Eagle, H Studies on Blood Coagulation The Nature of the Clotting Deficiency in Hemophilia, *J Gen Physiol* **18** 813, 1935

123 Howell, W H Theories of Blood Coagulation, *Physiol Rev* **15** 435, 1935

124 Kugelmass, I N "Bleeding" and "Clotting" Diets, *M Clin North America* **19** 989, 1935

125 Willie, H Ueber den Bau und die Funktion der Megakaryocyten und ihre Beziehungen zur thrombopenischen Purpura, *Folia haemat* **53** 426, 1935

cause, the thrombocytes being withdrawn from the circulation and fixed in the bleeding areas as a defense mechanism <sup>126</sup>

Both hereditary <sup>127</sup> and acquired <sup>128</sup> types of thrombocytopenic purpura have been described. In many instances the etiology is not known. Usually it is associated with disease of the bone marrow <sup>125</sup> or spleen or is the result of infection or drugs <sup>128d</sup>. Purpura associated with alterations in the permeability of the vascular membranes may be the result of allergy, <sup>129</sup> food deficiency, infection <sup>128a</sup> or toxins. The determination of the causal factor of purpura before institution of treatment is most important, and since this cannot always be accomplished failure of therapy may result.

Splenectomy, although usually associated with remarkable improvement in cases of thrombocytopenic purpura, may also be of no benefit <sup>130</sup>. If the spleen is overactive and destroys the platelets in excess numbers, its removal is indicated, however, if the decrease in the number of thrombocytes is the result of a disturbance in the production of platelets in the bone marrow, splenectomy is of little value. Because of the high mortality rate associated with splenectomy, ligation of the splenic artery has been recommended as a substitute.

Bleeding associated with food deficiency may be alleviated by a well balanced diet, especially one rich in vitamins and having a high protein and high fat content <sup>124</sup>. Foci of infection and sources of toxins should be removed. Successful results have been reported by desensitization and removal of the cause in persons with purpura due to allergy <sup>128</sup>. Viosterol and halibut liver oil are of no value <sup>131</sup>. Snake venom <sup>132</sup> has

<sup>126</sup> Rolleston, H. The History of Haematology, *Proc Roy Soc Med* **27** 1161, 1934

<sup>127</sup> (a) Bailey, F. R., and McAlpin, K. R. Familial Purpura. Report of Two Cases, *Am J M Sc* **190** 263, 1935. (b) Farber, Jason E. Familial Hemorrhagic Condition Simulating Hemophilia and Purpura Hemorrhagica, *Am J M Sc* **188** 815, 1934.

<sup>128</sup> (a) Traut, E. F. Hypersensitivity in Rheumatic Disease. Henoch's Purpura with Erythema Nodosum, Rheumatic Fever, Migraine, State of Hypersensitivity to Ingesta, *M Clin North America* **18** 1237, 1935. (b) Eyermann, C. H. Allergic Purpura, *South M J* **28** 341, 1935. (c) Brown, O. H. Purpura Hemorrhagica from Food Sensitization. Successful Treatment by Dietary Regulation and Use of Digestants, *Case Report, Southwestern Med* **19** 131, 1935. (d) Hudson, E. H. Purpura Haemorrhagica Caused by Gold and Arsenical Compounds, with Report of Two Cases, *Lancet* **2** 74, 1935.

<sup>129</sup> Eyermann <sup>128b</sup> Brown <sup>128c</sup>

<sup>130</sup> Unpublished data, Simpson Memorial Institute

<sup>131</sup> Jones, H. W., and Rathmell, T. K. Purpura Hemorrhagica. Effect of Viosterol on Blood Platelets, *Tr A Am Physicians* **49** 277, 1934.

<sup>132</sup> Peck, S. M., and Rosenthal, N. Effect of Moccasin Snake Venom (*Ancistrodon piscivorus*) in Hemorrhagic Conditions, *J A M A* **104** 1066 (March 30) 1935. Greenwald, H. M. Dilute Snake Venom for the Control of Bleeding in Thrombocytopenic Purpura, *Am J Dis Child* **49** 347 (Feb) 1935.



been employed in many instances. The results are conflicting, and there are insufficient data at present to estimate their clinical worth. Since spontaneous cure is not uncommon, a conservative attitude must be adopted concerning the value of the various therapeutic agents recommended.

#### HEMOPHILIA

Hemophilia is diagnosed by the following features: heredity, occurrence in males, a history of repeated hemorrhages,<sup>133</sup> prolonged clotting time and normal bleeding time. There is considerable diversity of opinion regarding the nature of the blood elements concerned with the clotting mechanism in hemophilia.<sup>134</sup> It was recently demonstrated that all the elements are normal but that the formation of thrombin is delayed.<sup>122</sup> Some authors have expressed the belief that the disease is due to faulty development of the liver, while others have stated that it is caused by an endocrine deficiency.

Included in the group of diseases associated with abnormal bleeding, there is described a syndrome known as hereditary pseudohemophilia.<sup>135</sup> It is characterized by the following features: heredity, transmission by either sex, normal platelet count, positive reactions to the Rumpel-Leed and needle-prick tests, prolonged bleeding time and normal clotting time.

The histopathologic structure of the hematopoietic tissues in cases of hemophilia is quite interesting.<sup>136</sup> Studies of the bone marrow reveal an increase in the number of megakaryocytes, which do not appear to vary from the normal in morphology. The red blood cell-forming and white blood cell-forming tissues likewise appear normal. No abnormalities are detected in the blood vessels. With the exception of the prominence of the reticulo-endothelial system, no changes are evident in the spleen or lymph glands.

At present no known specific therapy exists. Some of the common agents employed are whole blood, citrated blood, human plasma, human and animal serum, defibrinated blood, hemostatic preparations, fibrinogen and cephalin in suspension, calcium chloride, sodium citrate, protein shock, liver and its derivatives, whole ovary and ovarian extracts and

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133 Seligman, B. Hematuria in Hemophilia, with Two Cases of Acute Nephritis, *M Rec* **141** 150, 1935.

134 Quick, A. J. The Prothrombin in Hemophilia and in Obstructive Jaundice, *J Biol Chem* **109** 73, 1935. Quick, A. J., Stanley-Brown, M., and Bancroft, F. W. A Study of the Coagulation Defect in Hemophilia and in Jaundice, *Am J M Sc* **190** 501, 1935.

135 Handley, R. S., and Nussbrecher, A. M. Hereditary Pseudo-Haemophilia, *Quart J Med* **4** 165, 1935.

136 Custer, R. P., and Krumbhaar, E. B. The Histopathology of the Hemopoietic Tissues in Hemophilia. Unexplored Field, *Am J M Sc* **189** 620, 1935.

a special dietary regimen<sup>124</sup> This therapy may be employed as a prophylactic and as treatment for the immediate hemorrhage

Although it has been stated that the urine of persons with hemophilia does not contain the estrogenic hormone, all investigators do not agree with this fact<sup>137</sup> The results obtained in the prevention of the episodes of bleeding with ovary, ovarian extracts and other tissue extracts have not been encouraging<sup>138</sup> Sensitization with animal serum still remains the most satisfactory form of prophylactic therapy Acute hemorrhages are best treated by compression, multiple transfusions, administration of epinephrine, repeated injections of whole blood into the buttocks and local application of snake venom<sup>139</sup>

#### "BANTI'S DISEASE"

Banti in 1881 originally described the disease that is given his name as a distinct entity and stated that the course was divided into three stages, which lasted for several years In 1894 he reported a more complete series of cases and modified his views somewhat He postulated that the etiologic agent was an unidentified toxic substance carried to the spleen with secondary involvement of the liver The pathologic changes noted were sclerosis of the splenic vessels, atrophy of the malpighian corpuscles, induration of the pulp, sclerosis of the portal system and atrophic cirrhosis of the liver The treatment was splenectomy

At the present time the existence of this disease is questioned The pathologic changes which were thought to be specific by Banti have been produced experimentally<sup>140</sup> in animals by obstruction of the portal and splenic veins and have been demonstrated at autopsy to be secondary to hepatic disorders (cirrhosis) and thrombosis of the portal and splenic veins<sup>141</sup> It has been suggested that the syndrome be termed hepatolienal cirrhosis

The most commonly observed symptoms and signs are splenomegaly, weakness, hemorrhage, enlargement of the liver, jaundice and ascites Cases have been reported in which the patient had intermittent painful

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137 Chew, W B , Stetson, R P Smith, G V, and Smith, O W Estrogenic, Luteal and Gonadotropic Hormones in Hemophilia, *Arch Int Med* **55** 431 (March) 1935

138 Novak, E The Therapeutic Use of Estrogenic Substances, *J A M A* **104** 1815 (May 18) 1935 Chew, Stetson, Smith and Smith<sup>137</sup>

139 Peck, S M , Crimmins, M L, and Erf, L A Coagulating Power of Bothrops Atrox Venom on Hemophilic Blood, *Proc Soc Exper Biol & Med* **32** 1525, 1935

140 McMichael, J Splenic Anemia, *Edinburgh M J* **422** 97, 1935

141 Lemoff, H D Splenic Vein Thrombosis and Its Relationship to Banti's Syndrome, with Report of a Case, *Ann Int Med* **9** 85, 1935 McMichael<sup>140</sup>

joints in addition to the anemia and splenomegaly<sup>142</sup> The question has arisen whether arthritis is a coincidental finding, Fitz commented on the possible relationship of Banti's disease, Felty's syndrome, gout and Still's disease In another case report he discussed the relationship of peptic ulcer and Banti's disease<sup>143</sup>

The anemia present may be microcytic or macrocytic Unquestionably the former type is due to chronic hemorrhage Macrocytic anemia is probably the result of interference with hematopoiesis due to the failure of the liver to store or present for utilization to the bone marrow the substance necessary for the maturation of the red blood cells It is felt by some that the anemia is the result of an increase in hemolysis One author stated that in his particular case macrocytic anemia was due to a combination of changes in the thyroid and spleen<sup>144</sup> The nature of the anemia following splenectomy has been studied experimentally in rats<sup>145</sup> The investigator is of the opinion that the reticulo-endothelial system governs hematopoiesis and that hypochromic anemia resulting from the operation is due to a deficiency of hemoglobin Hyperplasia of the reticulo-endothelial system aids in the storage of iron, thus the administration of iron will lessen the severity of the anemia but will not eliminate it

For several years the accepted treatment for Banti's disease has been splenectomy A résumé of the early reports is confusing as in many of the cases reported the condition does not fit into this syndrome Furthermore, the disease itself may run a course lasting several years, so that any conclusions drawn concerning the benefits derived from this procedure must be guarded Recently many authors have again emphasized the value of splenectomy in cases of Banti's disease<sup>146</sup> The results obtained by workers at the University of Michigan Hospital<sup>147</sup> as well as those obtained by others,<sup>148</sup> do not seem to justify the con-

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142 Fitz, R Three Cases with Intermittently Painful Joints, Splenomegaly and Anemia, *M Clin North America* **18** 1053, 1935

143 Jennings, J E Duodenal Ulcer and Banti's Disease, Diaphragmatic Hernia, Hirsute Virilism, *Ann Surg* **102** 138, 1935

144 Serio, F Anemie tireosplenopatiche, *Haematologica* **16** 609, 1935

145 Gotthieb, R Nature of Postsplenectomy Anaemia, *Canad M A J* **32** 642, 1935

146 Larrabee, R C Chronic Congestive Splenomegaly and Its Relationship to Banti's Disease, *Am J M Sc* **188** 745, 1934 Ellis, R W B Anaemia Associated with Splenomegaly in Childhood, *Practitioner* **134** 317, 1935 Mills, E S Blood Dyscrasias Amenable to Treatment by Splenectomy, *Canad M A J* **33** 480, 1935 Leinoff<sup>141</sup> Jennings<sup>143</sup>

147 Goldhamer, S M Splenectomy in Hematopoietic Disorders, *Univ Hosp Bull Ann Arbor* **2** 20, 1936

148 (a) Watson, R B Ligation of Splenic Artery for Advanced Splenic Anaemia, *Brit M J* **1** 821, 1935 (b) McMichael<sup>140</sup>

tinuation of this type of treatment. Ligation of the splenic artery has been recommended when the condition is far advanced.<sup>148a</sup> The administration of iron before and after splenectomy is offered as a method to reduce the mortality rate.<sup>149</sup> Because of the high mortality rate associated with splenectomy and the equally good results following conservative measures, it appears that the latter type of therapy would be preferable.

#### GAUCHER'S DISEASE

Three members of a family, a sister and two brothers, were studied by Kveim.<sup>150</sup> The ages were 23, 26 and 28 years. The symptomatology included hepatomegaly, splenomegaly, leukopenia, thrombopenia, an increase in the rate of sedimentation, a tendency to bleed, subperiosteal hemorrhages, petechiae on the lower extremities and brown discoloration of the exposed parts of the body. Gaucher cells were found in the bone marrow. In the sister there was a black discoloration of the instep and leg almost up to the knees, apparently associated with the hemorrhagic diathesis.

Special features of Gaucher's disease have been emphasized in several case reports. Involvement of the kidneys and splenomegaly were reported by Horsley, Baker and Apperly,<sup>151</sup> Sichel and Warter,<sup>152</sup> and Merklen and Warter,<sup>153</sup> each reported a case in an adult. The pseudo-bulbar syndrome was reported in an infant by Meyer.<sup>154</sup> De Castro-Freire,<sup>155</sup> Acuña and de Filippi,<sup>156</sup> reported the effect of splenomegaly in a case. Cavazzutti, Cricco and Calandra<sup>157</sup> also reported a case.

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149 Davidson, L. S. P. Iron in Treatment of Splenic Anaemia, *Lancet* **2** 593, 1934.

150 Kveim, A. Three Cases of Gaucher's Disease, *Norsk mag f lægevidensk* **96** 696, 1935.

151 Horsley, J. S., Jr., Baker, J. P., Jr., and Apperly, F. L. Gaucher's Disease of Late Onset with Kidney Involvement and Huge Spleen, *Am J M Sc* **190** 511, 1935.

152 Sichel and Warter. Un cas de maladie de Gaucher chez l'adulte, *Bull et mem Soc de radiol med de France* **22** 509, 1934.

153 Merklen, P., and Warter, J. Esquisse de la maladie de Gaucher de l'adulte, *Medecine* **16** 233, 1935.

154 Meyer, R. Nouveau cas de syndrome pseudo-bulbaire du nourrisson (maladie de Gaucher du nourrisson), *Rev neurol* **2** 612, 1934.

155 de Castro-Freire, L. De la splenectomie dans la maladie de Gaucher, *Arch de med d enf* **38** 163, 1935.

156 Acuña, M., and de Filippi, F. Enfermedad de Gaucher en un lactante. Esplenectomia, *Semana med* **1** 735, 1935.

157 Cavazzutti, G. B., Cricco, J. J., and Calandra, R. Enfermedad de Gaucher, *Rev sud-am de endocrinol* **17** 865, 1934.

## NIEMANN-PICK'S DISEASE AND SCHULLER-CHRISTIAN'S SYNDROME

Esser<sup>158</sup> isolated diplococci from the blood of his patient with Niemann-Pick's disease Klenk<sup>159</sup> studied the nature of the phosphatids and other lipoids of the brain and liver of a patient with Niemann-Pick's disease

Radding<sup>160</sup> reported a case of Schuller-Christian's syndrome in which roentgen therapy was used, the patient was living and under observation for eleven years Teperson<sup>161</sup> treated his patient with roentgen rays In the cases of Smith<sup>162</sup> and Horsfall and Smith<sup>163</sup> the lesions of the bones were marked, and in the latter case there were exophthalmos and diabetes insipidus A number of cases were described by Livingston,<sup>164</sup> Fraser<sup>165</sup> and Dauksys<sup>166</sup> and by others during the year

## HODGKIN'S DISEASE LYMPHOBLASTOMA

A study of the numerous reports in the literature of cases of Hodgkin's disease revealed the condition in the following sites abdomen (Bargen and Ochsner<sup>167</sup>), nervous system (Cooper<sup>168</sup>), testes (Townsend<sup>169</sup>), urinary passages, spleen, nasopharynx and bones

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158 Esser, M Eigenartige bakteriologische Befunde im Blute eines Falles von Niemann-Pickscher Erkrankung, Zentralbl f Bakt (Abt 1) **134** 461, 1935

159 Klenk, E Ueber die Natur der Phosphatide und anderer Lipide des Gehirns und der Leber bei der Niemann-Pickschen Krankheit XII Mitteilung uber Phosphatide, Ztschr f physiol Chem **235** 24, 1935

160 Radding, M B Schuller-Christian Disease After X-Ray Therapy, Living and Under Observation Eleven Years, Radiology **24** 591, 1935

161 Teperson, H I Xanthomatosis Case of Schuller-Christian's Disease Treated by Irradiation, Radiology **25** 440, 1935

162 Smith, L A Xanthomatosis Involving Bone (Lipoid Histiocytosis) Case Reports and Roentgen Findings, Radiology **24** 521, 1935

163 Horsfall, F L, Jr, and Smith, W R Schuller-Christian Syndrome Lipoid-Granulomatosis with Defects in Bones, Exophthalmos, and Diabetes Insipidus, Quart J Med **4** 37, 1935

164 Livingston, S K Schuller-Christian Disease (Xanthomatosis) Case Report, J Bone & Joint Surg **17** 1035, 1935

165 Fraser, J Skeletal Lipoid Granulomatosis (Hand-Schuller-Christian's Disease), Liverpool Med-Chir J (pt 2) **42** 133, 1934, Brit J Surg **22** 800, 1935

166 Dauksys, J Xanthomatosis Schuller-Christian's Disease, J Missouri M A **32** 466, 1935

167 Bargen, J A, and Ochsner, H C Abdominal Hodgkin's Disease Report of a Case, M Clin North America **19** 423, 1935

168 Cooper, E L Hodgkin's Disease Some Clinical Aspects, with Special Reference to Effects upon Haemopoietic Tissues and Nervous System, M J Australia **1** 585, 1935

169 Townsend, W G Hodgkin's Disease of Testes, Urol & Cutan Rev **39** 853, 1935

(Livingston<sup>170</sup>), and sternum Thoracic involvement, amyloid degeneration, anemia, ocular lesions, paraplegia, diabetes insipidus and infiltration of the ureters with bilateral obstructive pyelonephritis (Beck<sup>171</sup>) were also reported in certain cases A case of the hepatic form was reported, and in 2 cases itching was a symptom (Craver,<sup>172</sup> Melton<sup>173</sup>)

Potter<sup>174</sup> has analyzed the lymphoblastomas in terms of the cells involved She subdivided Hodgkin's disease on this basis into endotheliomatous, reticular, cellular and sclerotic types Specific "Hodgkin's cells" must be present to confirm the diagnosis Hodgkin's disease, sarcoma arising from the reticulo-endothelium and leukemia are considered as three distinct entities

Pulmonary lymphogranulomatosis may be confused at times with tuberculosis, but there are certain roentgenographic appearances which may aid in the differential diagnosis Goia, Daniello and Hanganutz<sup>175</sup> noted that while the parenchymatous pulmonary lesions are not specifically characteristic, the constancy of mediastinal lesions and peribronchovesicular lymphangitis are diagnostic The opaque peribronchial adhesions are usually larger and more rounded than the tuberculous lesions, and the former lesions as well as the perifocal congestive reactions regress readily with roentgen irradiation

In Wheatley's<sup>176</sup> case Hodgkin's disease was kept under control for ten years with roentgen irradiation Paraplegia developed, but almost complete relief was obtained with irradiation therapy

In Loveman's<sup>177</sup> case cutaneous manifestations antedated the appearance of fever and adenopathy Roentgen therapy was effective The author considered that generalized exfoliative dermatitis or universal scaly erythroderma should always be regarded as a possible cutaneous

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170 Livingston, S K Hodgkin's Disease of Skeleton Without Glandular Involvement Case Report Proved by Autopsy, *J Bone & Joint Surg* **17** 189, 1935

171 Beck, D Hodgkin's Disease with Bilateral Obstructive Pyelonephritis Due to Infiltration of Ureters, *J Mount Sinai Hosp* **2** 126, 1935

172 Craver, L F Treatment of Itching in Hodgkin's Disease, *M Clin North America* **19** 967, 1935

173 Melton, R R Report of a Case of Hodgkin's Disease Presenting Pel Ebstein Type of Remittent Fever with Chills and Generalized Pruritis, *J Kansas M Soc* **36** 140, 1935

174 Potter, E L Hodgkin's Disease, with Special Reference to Its Differentiation from Other Diseases of Lymph Nodes, *Arch Path* **19** 139 (Feb) 1935

175 Goia, I, Daniello, L, and Hanganutz, M Considérations sur les formes pseudotuberculeuses de la lymphogranulomatose maligne, *Arch méd-chir de l'app respir* **10** 283, 1935

176 Wheatley, L F Lymphoblastoma with Paraplegia and Prolonged Irradiation, *J A M A* **104** 460 (Feb 9) 1935

177 Loveman, A B Cutaneous Manifestations of Lymphoblastomas Report of a Case of Hodgkin's Disease, *J A M A* **104** 1583 (May 4) 1935

manifestation of one of the lymphadenoses. In Wile and Stiles' <sup>178</sup> case, observed at intervals for at least thirteen years, the primary picture was that of mycosis fungoides, but characteristics of typical Hodgkin's disease ultimately developed, resulting in the patient's death. Comando <sup>179</sup> reported a case of primary isolated Hodgkin's disease, limited to the distal portion of the pars media and the proximal part of the pyloric portion of the stomach. A prolonged remission, without recurrence, followed removal of the lymphoblastomatous tissue.

Schwarz <sup>180</sup> stated that pregnancy and living at high altitudes are detrimental to patients with Hodgkin's disease. As opposed to large single doses of roentgen rays to circumscribed fields or total irradiation with a large dose, he outlined the treatment as follows: 1 Each focus should receive treatment. 2 Fractional doses should be given at intervals of one or two days. 3 The size of the field should not exceed 800 sq. cm. 4 The surface doses should not exceed 250 roentgens. 5 The controlling factors are the tolerance of the skin, the status of the blood and the general reaction, such as fever or nausea. 6 The appearance of new lesions should be noted. In cases in which the condition is refractory Schwarz gives thorium X, which, in combination with roentgen rays, may cause improvement in the patient's condition.

#### LEUKEMIA

*Symptomatology*—Schwab and Weiss <sup>181</sup> noted neurologic signs in 20.5 per cent of 334 cases of leukemia. There were neurologic signs in only about 25 per cent of the cases in which there was histologic evidence of leukemic infiltration of the central nervous system. There was unilateral or bilateral palsy of the sixth and seventh nerves, and less frequently of the fifth, eighth, ninth, tenth, eleventh and twelfth nerves. Among other signs were absence of deep reflexes, presence of signs referable to the pyramidal tract, paresthesias and evidence of meningeal irritation. The signs may show rapid fluctuations. Changes in the spinal fluid, present in 73.6 per cent of 34 cases, consisted of an increase in the cell count, an increase in the protein content and elevation of pressure.

The changes in the fundi may range from slight enlargement of the retinal veins to extreme retinitis. Leukemic infiltration of the orbital

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<sup>178</sup> Wile, U. J., and Stiles, F., Jr. Clinical Mutations in Lymphoblastomas, *J. A. M. A.* **104**: 532 (Feb. 16) 1935.

<sup>179</sup> Comando, H. N. Primary Isolated Lymphogranulomatosis of Stomach. Report of Case, *Arch. Surg.* **30**: 228 (Feb.) 1935.

<sup>180</sup> Schwarz, G. Ueber Röntgenbehandlung Lymphogranulomkranker, *Wien Arch. f. inn. Med.* **27**: 353 1935.

<sup>181</sup> Schwab, R. S., and Weiss, S. The Neurologic Aspect of Leukemia, *Am. J. M. Sc.* **189**: 766, 1935.

connective tissue may produce unioctal or binocular exophthalmos (Kreibig<sup>182</sup>) Symmetrical aleukemic lymphadenosis of the orbit was noted in a case reported by Dzigielewski<sup>183</sup> Gross papilledema may be present in chronic myelogenous leukemia (Frank<sup>184</sup>)

In 11 cases of leukemia, Goldstein and Wexler<sup>185</sup> found that the retinal lesions were minimal, marked sheathing of the veins with exudation of leukocytes into the retina and optic nerve, fragmentation and necrosis of the walls of the larger vessels and marked infiltration of the choroid were noted in exceptional patients Exophthalmos and edema of the conjunctivae may occur coincidentally with a marked increase in the blood count

Diamond<sup>186</sup> reported leukemic changes in the brain (14 cases), and Mills<sup>187</sup> correlated the observations in 60 cases of acute lymphatic leukemia in children

In reviewing the osseous changes in cases of lymphocytic, myelocytic and monocytic neoplasm, Doub and Hartman<sup>188</sup> summarized the observations as follows (1) punched-out areas of bone destruction (myelogenous leukemia, aleukemic myelosis, chloroma, Hodgkin's disease, and lymphosarcoma), (2) erosion in the ends of the diaphyses of the long bones (lymphatic leukemia, aleukemic myelosis, chloroma and Hodgkin's disease), (3) pinpoint areas of decalcification or destruction (aleukemic myelosis, chloroma, usually in the flat bones, e g, skull) and (4) erosion of the cortex from within the medullary canal (myelogenous leukemia) Other changes are osteosclerosis (aleukemic myelosis, Hodgkin's disease and myelogenous leukemia, occasionally in lymphatic leukemia), generalized osteoporosis (lymphatic leukemia, aleukemic myelosis and chloroma) In the differential diagnosis sympathetic neuroblastoma shows practically the same roentgenographic changes,

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182 Kreibig, William Ueber Bindehautveränderungen bei leukamischen Erkrankungen, *Ztschr f Augenh* **84** 120, 1934

183 Dzigielewski, K Ueber symmetrische aleukamische Lymphadenose der Orbita, *Ber u d Versamml d deutsch ophth Gesellsch* **50** 276, 1934

184 Frank, T J F Leuchaemic Retinitis Analysis of Eye Changes in Thirty-Five Cases of Leuchaemia, Together with Report of Gross Papilloedema in Case of Chronic Myelogenous Leuchaemia, *M J Australia* **1** 364, 1935

185 Goldstein, I, and Wexler, D Histologic Observations on the Fundus in Leukemia, *Arch Ophth* **13** 26 (Jan) 1935

186 Diamond, I B Leukemic Changes in Brain Report of Fourteen Cases, *Arch Neurol & Psychiat* **32** 118 (July) 1934

187 Mills, S D Acute Lymphatic Leucemia in Childhood Study of Sixty Cases with Especial Reference to Cytologic Characteristics of Blood, *J Pediat* **6** 634, 1935

188 Doub, H P, and Hartman, F W Lymphocytic, Myelocytic and Monocytic Neoplasms Roentgen Diagnosis and Treatment, *J A M A* **105** 942 (Sept 21) 1935



but metastatic carcinoma, multiple myeloma, osteogenic sarcoma, xanthomatosis, Gaucher's disease, Albers-Schonberg's disease and infection of the bone must be considered

Osseous changes were noted by Craver and Copeland<sup>189</sup> in about 7 per cent of 86 patients with lymphatic leukemia but in only 1 of a group of 84 patients with myelogenous leukemia

Baty and Vogt<sup>190</sup> studied the bones of 43 children roentgenographically. In 70 per cent there was a narrow zone of diminished density proximal to the metaphyses of the long bones. Two patients showed generalized osteoporosis, and 2 showed slight periosteal elevation. Neuroblastoma, with generalized milary metastasis, may show a roentgenographic picture similar to that of leukemia. The pathologic changes in the bones have been studied by Erb<sup>191</sup>

Abt<sup>192</sup> noted that leukemia during childhood presents certain difficulties in diagnosis. The diagnosis may be confused with that of diphtheria, ulcerative stomatitis, scurvy and endocarditis, pertussis, pneumonia, sepsis, von Jaksch's anemia, Cooley's Mediterranean erythroblastic anemia, infectious mononucleosis, mediastinal tumor, Niemann-Pick's essential lipoid histiocytosis, rheumatism, diarrhea, parotitis, appendicitis and aplastic anemia, but a thorough examination of the blood will usually serve to prevent a mistaken diagnosis. The acute types are more common in childhood, chronic myelogenous leukemia is seen occasionally and chronic lymphatic leukemia rarely. The symptoms in children include fever, headache, loss of appetite, vomiting, asthenia, progressive weakness and anemia, apathy, pain in the abdomen, bones or joints, bleeding (mucous membranes and skin), cervical adenopathy, stomatitis, nervous symptoms, occasional dyspnea and cough (mediastinal involvement), swelling of the submaxillary and lacrimal glands and leukemic infiltrations in the skin.

Fuchs<sup>193</sup> noted that the lymphocytosis and occasionally a palpable spleen during childhood may make the diagnosis of leukemia difficult. Severe pain, fever and inflammatory swelling of the joints may be observed. While enlargement of the lymph nodes may be present in association with arthropathy (acute articular rheumatism or Still's dis-

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189 Craver, L. F. and Copeland, M. M. Changes of Bones in Leukemias, *Arch Surg* **30** 639 (April) 1935

190 Baty, J. M., and Vogt, E. C. Bone Changes of Leukemia in Children, *Am J Roentgenol* **34** 310, 1935

191 Erb, I. H. Bone Changes in Leukaemia. Pathology, *Arch Dis Childhood* **9** 319, 1934

192 Abt, Arthur F. The Diagnosis of Leukemia in Childhood, *Pennsylvania M J* **38** 389, 1935

193 Fuchs, B. Ueber Gelenkerscheinungen bei kindlicher Leukamie, *Monatsschr f Kinderh* **63** 185, 1935

ease), it should suggest study for leukemia. Areas of lesser density in the bones may be confirmatory of the diagnosis of leukemia. Osteitis fibrosa and Gaucher's disease may show similar roentgenographic changes.

Dumitrescu and Petrea<sup>194</sup> described a case of acute leukemia which simulated acute articular rheumatism.

Pain in the joints, without visible evidence of inflammation in children with leukemia, may sometimes make the differentiation from rheumatic disease difficult, unless the blood picture is characteristic. The pains may be migratory and vague, without evidence of changes roentgenographically. Smith<sup>195</sup> suggested that in the initial stages pain is due to increased pressure within the bone from the crowding of the hyperplastic marrow. The second step is rarefaction of the bone, followed by elevation of the periosteum from the spread of leukemic cells. Abnormal lymphocytes of a specific type may be present in the peripheral blood of patients of this type. Sutton and Bosworth<sup>196</sup> reported a case of lymphatic leukemia resembling rheumatic fever in a child.

In the diagnosis of leukemia, especially in the absence of characteristic changes in the blood, material obtained by sternal puncture (Lowinger<sup>197</sup>) or by splenic puncture (Perles,<sup>198</sup> Weil, Isch-Wall and Perles,<sup>199</sup> Papafotis<sup>200</sup>) may be of aid in determining the nature of the disease. Cells may be identified by the quantitative oxidase reaction (Nagel<sup>201</sup>), by the presence of Auer bodies (Lovisato,<sup>202</sup> Hawksley<sup>203</sup>), by the supravital staining characteristics (Lightwood, Hawksley

194 Dumitrescu, T, and Petrea, C. Leucémie aigue simulant le rhumatisme, Bull et mem Soc med d hôp de Paris **50** 957, 1934.

195 Smith, C. H. Leucemia in Childhood with Onset Simulating Rheumatic Disease, J. Pediat **7** 390, 1935.

196 Sutton, L. P., and Bosworth, O. Lymphatic Leucemia Resembling Rheumatic Fever in Child. Report of Case, J. Pediat **5** 61, 1934.

197 Lowinger, S. Clinical Importance of Sternal Puncture. Bone Marrow Picture of Acute Myeloblastic Leukemia Associated with Leukopenia, Gyógyaszat **75** 455, 1935.

198 Perles, S. La ponction de la rate dans les maladies du sang, Paris méd **2** 217, 1935.

199 Weil, P. E., Isch-Wall, P., and Perles, S. La ponction de la rate dans la myelomatose, Sang **9** 347, 1935, Un cas de leucémie aigue sans modifications sanguines diagnostique par la ponction de la rate, *ibid* **9** 213, 1935.

200 Papafotis, C. La ponction de la rate et son importance pour l'étude etiologique des leucemies, Bull med, Paris **49** 399, 1935.

201 Nagel, W. Untersuchungen über den quantitativen Oxydasegehalt der neutrophilen Blutleukocyten bei akuten Infectionen und leukamischen Myelosen, Verhandl d deutsch Gesellsch f inn Med **47** 228, 1935.

202 Lovisato, L. Tre casi di leucemia acuta con corpi di Auer, Minerva med **2** 84, 1935.

203 Hawksley, J. C. Note on Occurrence of Auer's Bodies in Monocytic Leukaemia, J. Path & Bact **40** 365, 1935.

and Bailey <sup>204</sup>) or by peculiar inclusions in nonmature leukocytes (Yanonsky <sup>205</sup>)

Leukemia was first discovered in a patient of Rosler's <sup>206</sup> after trauma. Priapism was a marked feature. Improvement followed irradiation and the administration of arsenic. The author said that malaria, gas poisoning or trauma may cause leukemia, his patient was exposed to all three agents.

Carnot, Caroli and Busson <sup>207</sup> found splenic puncture a valuable aid in the diagnosis of aleukemic myelomatosis. In this condition there is a hepatosplenic association in the pathologic process which is characteristic of the disease.

Flinn <sup>208</sup> described a case of acute lymphatic leukemia of eight months' duration in a child of 4 years. There was a stage of extreme neutropenia, with slight but definite improvement after pentnucleotide therapy. An attack of rubella appeared to initiate a leukopenic phase, while a final leukemic stage accompanied an attack of acute follicular tonsillitis.

Bertelsen <sup>209</sup> described a case of acute leukemia in a 2 months old infant.

Jørgensen <sup>210</sup> reported a case of lymphatic leukemia in a shoemaker. The rôle of gaseous toxic substances, such as benzene, was considered. There was hyperplasia of all the preformed lymphatic tissue in all the organs.

De Marval <sup>211</sup> presented data that favor the infection theory of the origin of leukemia.

Weinstein and Fitz-Hugh <sup>212</sup> found that a low or normal titer of heterophile antibody is characteristic of leukemia, Hodgkin's disease, lymphosarcoma, polycythaemia vera, agranulocytic angina, typhoid,

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204 Lightwood, R., Hawksley, J. C., and Bailey, U. M. Supravital Staining in Diagnosis of Leukemias, *Proc Roy Soc Med* **28** 405, 1935.

205 Yanonsky, D. Des inclusions particulieres dans les leucocytes non mûrs dans les cas de leucemie aigue, *Sang* **9** 610, 1935.

206 Rosler, O. Traumatische Leukämie und Priapismus, *Munchen med Wchnschr* **82** 217, 1935.

207 Carnot, P., Caroli, J., and Busson, A. La myelose hepatosplenique aleucémique. Son diagnostic par la ponction de la rate, *Paris med* **1** 449, 1935.

208 Flinn, L. B. Acute Lymphatic Leukemia in a Child of Four Years with Severe Granulopenic Stage Preceding Remission, *Ann Int Med* **9** 458, 1935.

209 Bertelsen, A. Case of Acute Leukemia in Infant Two Months Old, *Ugesk f læger* **97** 798, 1935.

210 Jørgensen, J. Vesterdal. Case of Acute Lymphatic Leukemia with Extensive Infiltrates in Gastro-Intestinal Canal, *Ugesk f læger* **97** 327, 1935.

211 De Marval, L. Remisión, estado de equilibrio y recidiva en la leucemia meloide crónica, *Actas y trab d Cong nac de med* **3** 789, 1934.

212 Weinstein, G. L., and Fitz-Hugh, T., Jr. The Heterophile Antibody Test in Leukemia and Leukemoid Conditions, *Am J M Sc* **190** 106, 1935.

simple adenitis, syphilis, tuberculosis and anemia. Slight increase in the heterophile antibody was noted in the serum of a patient with acute leukemia who had received twenty-eight transfusions of blood. High titers were noted in serum sickness and acute infectious mononucleosis. The parenteral administration of horse serum raised the titer in patients with chronic myelogenous leukemia and in nonleukemic persons, but not in patients with chronic lymphatic leukemia and lymphosarcoma or in a patient with atypical Hodgkin's disease.

Henschen and Jezler<sup>213</sup> found the enlargement of the liver and spleen to be of aid in the differential diagnosis between aleukemic leukemia and the aplastic forms of anemia, especially in those cases in which but few immature cells appear in the blood stream.

In cases of malignant tumors of lymphoid organs, Rubnitz<sup>214</sup> found that cells may enter the blood stream and give a leukemoid picture. In the early stages the other blood elements are normal, differentiating this condition from true leukemia, but in the advanced stages, with the involvement of the entire hematopoietic apparatus, the picture becomes more like that of a true leukemia. Lymphosarcoma is more likely to give a leukemoid reaction than epithelial tumors.

From specimens of lymph nodes taken for biopsy during the course of the disease in a patient with lymphatic leukemia, Stasney and Downey<sup>215</sup> concluded. The first step in the leukemic process is a diffuse proliferation of reticulum. The blood picture parallels the histologic changes in the glands, with predominance of specific cell types. The syncytial reticulum cells retain an embryonic hematopoietic potency.

The renewed interest in agranulocytosis has called forth many reports on the agranulocytic phases of leukemia and the differential diagnosis from the true malignant neutropenia (Jackson,<sup>216</sup> Julliard,<sup>217</sup> Kerlin,<sup>218</sup> Mitchell and Ramey,<sup>219</sup> Monfort,<sup>220</sup> Reaud and Prado,<sup>221</sup>

213 Henschen, C, and Jezler, A. Aleukämische Myelose unter dem Bilde der Panmyelophthase, *Ztschr f klin Med* **128** 343, 1935.

214 Rubnitz, A. S. Atypical Leukemic States and Leukemoid Reactions, *Nebraska M J* **20** 287, 1935.

215 Stasney, J, and Downey, H. Subacute Lymphatic Leukemia. Histogenetic Study of Case with Three Biopsies, *Am J Path* **11** 113, 1935.

216 Jackson, H, Jr. Differential Diagnosis of Agranulocytic Angina from Acute Leukemia, *Am J M Sc* **188** 604, 1934.

217 Julliard. Agranulocytose et leucémie monocytes au cours d'une angine nécrotique avec nécrose pulmonaire terminale, *Arch d mal du cœur* **28** 311, 1935.

218 Kerlin, W. S. Differential Diagnosis Between Agranulocytic Angina and Acute Leukemia, *New Orleans M & S J* **87** 759, 1935.

219 Mitchell, E. W, and Ramey, W. O. Case of Aleukemic Leukemia Simulating Agranulocytosis, *J Med* **15** 602, 1935.

220 Monfort, R. Aplastic Anemia Blood Picture in Splenic Type of Acute Aleukemic Leucemia, *M Rec* **142** 123, 1935.

221 Reaud, A, and Prado, G. ¿Agranulocitosis a leucemia mieloblastica? *Rev de med y cir de la Habana* **40** 456, 1935.

Usseglio and Olivetti,<sup>222</sup> Wells,<sup>223</sup> Ederle and Esche,<sup>224</sup> Goldburgh<sup>225</sup>)

Stephens<sup>226</sup> described a fatal case of acute eosinophilic leukemia in a girl of 17 years. There was evidence of extramedullary production of eosinophils with suppression of adequate production of neutrophils.

*Leukemia in Animals*—Furth, Ferris and Reznikoff<sup>227</sup> considered that leukemia in man is essentially the same disease as in mice. The acute and chronic forms, both myelogenous and lymphatic, are neoplastic processes, and like cancer the etiology may be multiple, with intrinsic genetic as well as extrinsic genetic factors.

An authoritative summary of the present knowledge of mammalian leukemia, especially in mice, was presented by Richter and MacDowell<sup>228</sup>.

Furth<sup>229</sup> was able to transmit myeloid leukemia from one mouse to another by inoculation with tissue containing living cells (basophilic myelocytes). Inoculation was successful in almost every mouse after it was treated with roentgen rays. The malignant immature granulocytes may produce systemic diffuse disease or localized tumors (multiple myeloma). Experiments suggest that the transmitting mechanism is not a virus. The author considered that transmissible myeloid leukemia of mice is a neoplasm and that factors in its propagation are (a) the resistance of the host, (b) the route of entry, (c) the character of the malignant cell and (d) the inoculating dose. De Marval<sup>211</sup> stated, however, that human leukemia is an infectious process.

Lymphoid and myeloid infiltrations developed in 95 per cent of mice with spontaneous mammary carcinoma. The total irradiation of mice with cancer with small doses of roentgen rays resulted in a more marked increase in the incidence of leukemia than normally occurred in this

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222 Usseglio, G, and Olivetti, R. Sui rapporti tra leucemie acute e mielosi aplastiche (Nota critica su un caso di linfadenosi acuta con mielosi globale pseudoaplastica terminale), *Minerva med* **1** 183, 1935.

223 Wells, J. J. Acute Myelogenous Aleukemic Leukemia with Simulated Agranulocytosis. Report of Case, *U S Nav M Bull* **33** 527, 1935.

224 Ederle, W, and Esche, G. Agranulocytose und Leukämie, *Folia haemat* **52** 179, 1934.

225 Goldburgh, H. L. Aleukemic Leucosis. Report of Case of Myelogenous Leucemia in Aleukemic Phase with a Neutrophilic Angina and Recovery from Latter State, *M Rec* **140** 496, 1934.

226 Stephens, D. J. Acute Eosinophilic Leukemia, *Am J M Sc* **189** 387, 1935.

227 Furth, J, Ferris, H. W, and Reznikoff, P. Relation of Leukemia of Animals to Leukemia of Man, *J A M A* **105** 1824 (Dec 7) 1935.

228 Richter, Maurice N, and MacDowell, E. C. Experiments with Mammalian Leukemia, *Physiol Rev* **15** 509, 1935.

229 Furth, J. Transmission of Myeloid Leukemia of Mice. Its Relation to Myeloma, *J Exper Med* **61** 423, 1935.

strain of mice. Observations indicated that hyperplastic myeloid or lymphoid proliferations were transformed into leukemic ones after roentgen irradiation in susceptible mice (Hueper<sup>230</sup>). This is of interest in connection with the report of Kugelmeier<sup>231</sup> of the occurrence of a leukemoid reaction in 2 patients with carcinoma of the stomach and of Schreiner and Wehr<sup>232</sup> on cancer associated with leukemia (see also Paviot, Guichard and Plauchu,<sup>233</sup> Oberling and Guérin<sup>234</sup>). The rôle of heredity in spontaneous mouse leukemia was reported by MacDowell and Richter<sup>235</sup> and by MacDowell, Taylor and Potter<sup>236</sup>. Leukemia coincident with and transmissible by spindle cell sarcoma in mice was reported by Parsons<sup>237</sup>.

MacDowell, Taylor and Potter<sup>238</sup> demonstrated that susceptible mice may be immunized to transplantable leukemia by treatment with small numbers of leukemic cells. Later Rhoads and Miller<sup>239</sup> showed that a similar effect can be produced by the injection of normal lymphoid cells. When malignant cells are injected into immunized subjects, they first proliferate and then undergo degeneration. Immunity to transplantable mouse leukemia is, then, not the result of blockade or invasion of lesions by normal host lymphocytes, as the injected cells are necrotic before the mobilization of host cells takes place (Potter and Findley<sup>240</sup>).

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230 Hueper, W. C. Leukemoid and Leukemic Conditions in White Mice with Spontaneous Mammary Carcinoma, *Folia haemat* **52** 167, 1934.

231 Kugelmeier, L. M. Leukamoide Reaktionen bei Carcinom, *Folia haemat* **53** 370, 1935.

232 Schreiner, B. F., and Wehr, W. H. Cancer Associated with Leukemia, *Am J Cancer* **21** 368, 1934.

233 Paviot, J., Guichard, A., and Plauchu, M. Sur une forme particulière de cancer secondaire des os. Les anémies cancéreuses avec myélemie, *J de méd de Lyon* **16** 45, 1935.

234 Oberling, C., and Guérin, M. Leucémie et cancer. Etude expérimentale, *Rev med franç* **15** 755, 1934.

235 MacDowell, E. C., and Richter, M. N. Mouse Leukemia. Rôle of Heredity in Spontaneous Cases, *Arch Path* **20** 709 (Nov) 1935.

236 MacDowell, E. C., Taylor, M. J., and Potter, J. S. Dependence of Protection Against Transplantable Mouse Leukemia upon Genetic Constitution of Immunizing Tissue, *Proc Nat Acad Sc* **21** 507, 1935.

237 Parsons, L. D. Leukaemia Coincident with and Transmissible by Spindle-Cell Sarcoma in Mouse, *J Path & Bact* **40** 45, 1935.

238 MacDowell, E. C., Taylor, M. J., and Potter, J. S. Immunization of Mice Naturally Susceptible to Transplantable Leukemia, *Proc Soc Exper Biol & Med* **32** 84, 1934.

239 Rhoads, C. P., and Miller, D. K. Induced Resistance to Transmissible Leukemia in Mice, *Proc Soc Exper Biol & Med* **32** 817, 1935.

240 Potter, J. S., and Findley, M. D. Histological Observations on Resistance to Transplantable Leukemia in Immunized Mice, *Proc Soc Exper Biol & Med* **32** 1338, 1935.

The subject of leukemia and lymphomatosis in fowls has received much study (Stubbs and Furth,<sup>241</sup> Furth,<sup>242</sup> Engelbreth-Holm,<sup>243</sup> Engelbreth-Holm and Meyer,<sup>244</sup> Engelbreth-Holm, Meyer and Uhl,<sup>245</sup> Meyer, Engelbreth-Holm and Uhl,<sup>246</sup> Wallbach<sup>247</sup>)

The virus of chicken leukosis (strain 2) produces a neoplastic growth of lymphocytes but does not produce a tumor at the site of injection when given intramuscularly. Two transmissible strains of the virus of neurolymphomatosis have been isolated, one produces no blood changes or "erythroleukosis" with myeloblastic leukemia, and the other, anemia with an increase in the number of large lymphocytes and occasionally myelocytes (Furth<sup>248</sup>). The transmitting agent is inactivated by freezing at  $-30^{\circ}\text{C}$  for thirty minutes or by drying from the frozen state.

Bernard<sup>249</sup> produced a leukemoid condition and a tumor of the bone by intramedullary injections of tar into apes.

*Monocytic Leukemia*—Mann<sup>250</sup> reported that splenomegaly and generalized lymphadenopathy may be present in only half of the cases of monocytic leukemia. At first there is a period of a few months in which infection, progressive pallor and lassitude are the most marked features. This is followed by ulcerative stomatitis and ulceration of the gums, local lymphadenopathy and rapid deterioration of the patient. With

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241 Stubbs, E. L., and Furth, J. Relation of Leucosis to Sarcoma of Chickens. *Sarcoma and Erythroleukosis (Strain 13)*, J. Exper. Med. **61** 593, 1935.

242 Furth, J. Studies on Effect of Roentgen Rays on Lymphomatosis of Mice, *Am. J. Roentgenol.* **32** 377, 1934.

243 Engelbreth-Holm, J. Experimental Studies on Transplantable Leukosis of Fowl, *Biblioth. læger.* **127** 119, 1935.

244 Engelbreth-Holm, J., and Meyer, A. R. Variation in Percentage of Takes in Three Strains of Chicken Leukosis, *Acta path. et microbiol. Scandinav.* **12** 366, 1935.

245 Engelbreth-Holm, J., Meyer, A. R., and Uhl, E. On Chemotherapy in Leucosis of Fowls, *Acta path. et microbiol. Scandinav.* **12** 491, 1935.

246 Meyer, A., Rothe, Engelbreth-Holm, J., and Uhl, E. Further Studies on Agent of Chicken Leukosis, *Acta path. et microbiol. Scandinav.* **12** 378, 1935.

247 Wallbach, G. Recherches sur la leucémie des poules. Variation de la symptomatologie selon les modifications expérimentales du virus, *Sang.* **9** 445, 1935, Recherches sur la leucémie des poules. Retentissement sur l'organisme de modifications apportées aux facteurs expérimentaux, *ibid.* **9** 553, 1935, Recherches sur la leucémie des poules. Les formes atypiques de la leucémie des poules, *ibid.* **9** 566, 1935.

248 Furth, J. Lymphomatosis in Relation to Fowl Paralysis, *Arch. Path.* **20** 379 (Sept.) 1935.

249 Bernard, J. Etat leucémoïde et tumefaction osseuse provoqués chez le singe par les injections intramedullaires de goudron, *Sang.* **9** 790, 1935.

250 Mann, W. N. Case of Monocytic Leukemia, *Guy's Hosp. Rep.* **85** 178, 1935.

this a leukemic blood picture develops, with many mature monocytes as well as immature forms

Mitchell<sup>251</sup> presented the report of a case of malignant monoblastoma, as a variant of monocytic leukemia, and reviewed the reports of 42 cases in the literature. The patient described had an aleukemic and a leukemic phase. There were multiple recurring monoblastomas which were formed by localized hyperplasia of the histiocytes of the diffuse connective tissues. Mercer<sup>252</sup> found a diffuse exanthematous eruption in 2 cases of monocytic leukemia. The lesions were slightly red macules and papules, changing to slate blue, and firmer pale papules deeper in the skin. Many of the lesions were transient, but some become necrotic.

Whitby and Christie<sup>253</sup> described the case of a patient with acute monocytic leukemia in which there were two remissions. The anemia was out of proportion to the apparent degree of the leukemic process. The necrotic lesions in the mouth were more on the alimentary mucous membranes than on the respiratory part of the pharynx, the ulceration not involving the tonsil or the nasal mucous membrane. During much of the course there was granulopenia. Hepatomegaly accompanied the appearance of a frankly leukemic blood picture, without enlargement of the spleen and lymph nodes. Studies of the spleen did not show evidence of proliferation of reticulum cells or of desquamation of histiocytes into the blood.

In a case of monocytic leukemia described by Haining, Kimball and Janes,<sup>254</sup> a leukemic mass in the rectal wall produced complete intestinal obstruction simulating carcinoma of the rectal wall. The authors considered monocytic leukemia as a sinus reticulosis and myelogenous and lymphatic leukemia as a true reticulosis.

Kracke and Garver<sup>255</sup> discussed the present views on leukemia. They stated that the chief cell type in monocytic leukemia has its origin in the bone marrow, and this theory is presented as evidence that monocytic leukemia is an atypical phase of myelogenous leukemia.

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251 Mitchell, Louis A. Malignant Monoblastoma. A Variant of Monocytic Leukemia, *Ann Int Med* **8** 1387, 1935.

252 Mercer, S. T. Dermatoses of Monocytic Leukemia, *Arch Dermat & Syph* **31** 615 (May) 1935.

253 Whitby, L. E. H., and Christie, J. M. Monocytic Leukaemia, *Lancet* **1** 80, 1935.

254 Haining, R. B., Kimball, T. S., and Janes, O. W. Leukemic Sinus Reticulosis (Monocytic Leukemia) with Intestinal Obstruction. Report of Case with Partial Autopsy, *Arch Int Med* **55** 574 (April) 1935.

255 Kracke, R. R., and Garver, H. Differential Diagnosis of Leukemic States, with Particular Reference to Immature Cell Types, *J A M A* **104** 697 (March 2) 1935.



Details of cutaneous eruptions in chronic cases of lymphatic leukemia (Miyamoto and Shikuma<sup>256</sup>) and of other forms (Saslawsky and Ioffe<sup>257</sup>) have been described

*Treatment*—Various forms of roentgen therapy have been evaluated Langei,<sup>109</sup> basing his treatment on the hypothesis that leukemia is the result of overactivity of the sympathetic nervous system, advocated roentgen therapy over the paravertebral ganglions (spinal column) The principles and technic of irradiation have been studied by Nisbet,<sup>110</sup> Pohle,<sup>258</sup> Rosselli del Turco,<sup>259</sup> Erickson and Dittmer,<sup>260</sup> Feuerstein<sup>261</sup> and Huguet<sup>262</sup>

High voltage roentgen ray therapy combined with lead therapy was tried by Schmahl<sup>263</sup> Arzt<sup>264</sup> uses radium therapy

Kalapos<sup>265</sup> studied the effect of the administration of benzene in cases of leukemia, and Krebs and Clemmesen<sup>266</sup> reported on the use of lead compounds Lucia<sup>267</sup> used a 1 per cent solution of antimony and potassium tartarate in sterile distilled water intravenously in progressive graded doses of 2, 3 and 5 cc on alternate days There was a marked reduction in the number of white blood cells in 6 of 9 patients with chronic myelogenous, chronic lymphatic and advanced monocytic

256 Miyamoto, Y, and Shikuma, K Ueber einen Fall von chronischer lymphatischer Leukämie mit einen selten beobachteten Hautsymptome, Nagasaki Igakkwai Zasshi **13** 814, 1935

257 Saslawsky, A, and Ioffe, E Skin Eruptions in Leukemia, Urol & Cutan Rev **39** 331, 1935

258 Pohle, E A Radiation Therapy in Medical Practice Leukemia, Hodgkin's Granuloma and Allied Diseases, Wisconsin M J **34** 632, 1935

259 Rosselli del Turco, L Il meccanismo di azione dei raggi roentgen sull'emopoiesi, in rapporto ad una eventuale terapia chimica delle leucemia, Riv di clin med **35** 863, 1934

260 Erickson, L G, and Dittmer, M G X-Ray Therapy in Leukemia, J Iowa M Soc **25** 553, 1935

261 Feuerstein, B L Radiation in Leucemia Report of Seventy-Seven Cases so Treated, M Rec **140** 492, 1934

262 Huguet De l'influence des rayons X sur le nombre des globules rouges dans les leucemies, Marseille med **2** 684, 1934

263 Schmahl, P J R Myelogenous Leukemia, J Am Inst Homeop **28** 75, 1935

264 Arzt, L Das Radium in der Therapie der Leukämien, Wien klin Wchnschr **48** 166, 1935

265 Kalapos, I Die Wirkung des Benzols bei der Leukämie, Klin Wchnschr **14** 864, 1935

266 Krebs, C, and Clemmesen, J Die Bleiverbindungen R232 und R237b verwendet bei der experimentellen Therapie von Tumoren und Leukose, Ztschr f Krebsforsch **41** 260, 1934

267 Lucia, S P Effects of Tartar Emetic on Leukocyte Count, Proc Soc Exper Biol & Med **32** 1109, 1935

leukemia, Hodgkin's disease and eosinophilic leukocytosis. The size of the lymph nodes and spleen, however, was not affected.

Desjardins<sup>268</sup> has summarized the present status of the treatment of leukemia as follows:

In acute leukemia, exposure to roentgen rays or radium is seldom followed by perceptible improvement, and experienced radiologists usually do not encourage such treatment. In the subacute form cautious treatment, and in the chronic form thorough treatment, yield more or less marked improvement for periods varying from months to several years. Usually the treatment must be repeated from time to time, depending on the numerical behavior of the leukocytes and on the tendency of the spleen or lymph nodes to enlarge. Effective treatment can be given with roentgen rays or radium. At the outset, and when extensive areas require irradiation, roentgen rays are preferable.

In myeloid leukemia the rays are directed first to the spleen, and then, if this is not sufficient to reduce the number of leukocytes approximately to the normal level, the mediastinum and long bones also may be irradiated. When the spleen is large, the surface of the abdomen corresponding to that organ may be divided into a number of fields, approximately 10 cm square, and each field should be exposed to a moderate dose of roentgen rays. If radium is used to irradiate the enlarged spleen, a large pack is required. The effect of treatment on the leukocytes should be followed closely by daily or frequent blood counts. When the number of leukocytes diminishes rapidly, the number of fields irradiated each day should be correspondingly reduced, otherwise, an excessive leukopenia may result. An abnormally small number of erythrocytes at the outset need not be regarded as a contraindication, under treatment the number of these cells tends to increase as the number of leukocytes diminishes. After a patient has been treated a number of times at intervals of months, the effectiveness of treatment tends to diminish, but this varies considerably from patient to patient. If the patient cooperates faithfully, the disease may often be kept under control for prolonged periods, sometimes for many years.

In lymphoid leukemia the treatment is directed first to the main groups of lymph nodes in the neck, axillae and groins, as well as to the mediastinal and retroperitoneal lymph nodes. If, by the time these several regions have been irradiated, the number of leukocytes has not diminished sufficiently, additional treatment to the shaft of the major long bones may have to be given.

Splenectomy has been resorted to by some (de Marval and Bomchil,<sup>269</sup> de Marval, Simonetti and Bomchil,<sup>270</sup> Becker<sup>271</sup>), but Rosenthal and Harris<sup>272</sup> advised against it. The value of transfusions of blood, the administration of arsenic and roentgen irradiation was

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<sup>268</sup> Desjardins, A. U. Radiotherapy (Roentgen Rays, Radium), *J. A. M. A.* **105** 2152 (Dec. 28) 1935.

<sup>269</sup> de Marval, L., and Bomchil, G. Esplenectomia en la leucemia, *Semana med.* **1** 1289, 1935.

<sup>270</sup> de Marval, L., Simonetti, C., and Bomchil, G. Esplenectomia en la leucemia, *Semana med.* **2** 261, 1935.

<sup>271</sup> Becker, A. Milzentirpation bei Leukämie, *Zentralbl. f. Chir.* **62** 1461, 1935.

<sup>272</sup> Rosenthal, N., and Harris, W. Leukemia. Its Diagnosis and Treatment, *J. A. M. A.* **104** 702 (March 2) 1935.

reiterated In cases of leukopenia radiotherapy is of no value in reducing the size of the spleen and is contraindicated in cases of severe leukopenia as it may be followed by secondary infection, necrosis and hemorrhage Arsenic may be employed advantageously between roentgen treatment The authors stated that irradiation is justifiable and useful in the treatment of acute leukemia, but they advised that transfusions of blood also be given

In a case of myelogenous leukemia and intraperitoneal hemorrhage, the spleen was removed A remission of several months followed, and in subsequent relapses roentgen irradiation was employed Death occurred fifteen months after splenectomy from strangulation ileus The case reported by Popper<sup>273</sup> illustrates the fact that splenectomy may be performed when an emergency requires it but that the course of the disease is not grossly influenced by the procedure

Israels<sup>274</sup> did not note beneficial effects of iodine, such as Friedgood had obtained, in 5 cases of chronic lymphatic leukemia He did note a moderate improvement in the white blood cell count, which he attributed to the direct action of iodine on the leukocytes and not on any fundamental leukemic mechanism He therefore does not see any evidence to justify thyroidectomy in this disease

In an effort to see if the deficiency of certain substances was the cause of chronic myelogenous leukemia, Castle, Meyer and Chew<sup>275</sup> tried desiccated mucosa of the stomach and small intestine, desiccated hog pancreas and mixtures of most of the fresh organs of newly born rabbits, with no improvement in the condition of the patients Daily transfusions of the plasma or whole blood of normal persons was not effective

#### INFECTIOUS MONONUCLEOSIS

In 1885 Filatow originally described an idiopathic lymphadenopathy Pfeiffer in 1889 commented on an acute disease occurring in children, characterized by fever, enlargement of glands and changes in the blood, and called it glandular fever Desplats in 1894 noted the involvement of the axillary and inguinal glands as well as of the glands in the cervical region In the same year Horschelmann observed a scarlatina-like eruption during the course of the disease West first described the disease in the United States in 1896, and Williams originally described it in England in 1897 Sprunt and Evans in 1920 and Longcope in 1922

273 Popper, H L Splenektomie bei Leukämie, *Med Klin* **31** 615, 1935

274 Israels, M C G Treatment of Lymphatic Leukaemia with Special Reference to Use of Iodine, *Brit M J* **1** 1021, 1935

275 Castle, W B, Meyer, O O, and Chew, W B Negative Results of Treatment of Chronic Myelogenous Leukemia as a Deficiency Disease, *Proc Soc Exper Biol & Med* **32** 660, 1935

established the disease on a more secure clinical basis and termed it "infectious lymphocytosis" and "infectious mononucleosis," respectively. Most accurate and detailed descriptions of the changes in the blood were made by Downey and McKinlay in 1923.

Various organisms have been isolated and described <sup>276</sup> as the etiologic factor of infectious mononucleosis, but none of them has ever been confirmed by others than the original investigators. Sporadic and epidemic cases have been observed in Europe, North America, China, Australia and the Falkland Islands, but only 3 cases have been noted in the Tropics. Apparently the disease occurs in either sex and at any age, though it is more common in children and in persons under 40. The prodromal period varies, depending on the type of disease <sup>276a</sup>. In the glandular type, the prodromal period is from one to four days, and in the angiose type, from one to three weeks. The period of incubation is described by some as from seven to eight days <sup>276d</sup>.

The more common symptoms, as observed by various clinicians, <sup>277</sup> are headache, general malaise, sore throat, tenderness of the glands, backache, chilliness, anorexia, coryza, sweating, weakness, cough, dizziness, sore bleeding gums, nausea, stiff neck, epistaxis, stomatitis, abdominal pain, rash, photophobia and conjunctivitis. The physical signs usually encountered are fever, enlargement and tenderness of the glands, injection of the throat, enlargement of the spleen, enlargement of the tonsils, membranous angina and a maculopapular rash. The temperature usually varies between 101 and 105 F. Enlargement of the glands is present in 100 per cent of the cases and tenderness in 76 per cent. Suppuration of the glands has seldom been observed.

The complications which are encountered are variable: sepsis, hematuria, purpura, jaundice, appendicitis, meningismus and involvement of the respiratory tract.

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<sup>276</sup> (a) Tidy, H. L. Glandular Fever and Infectious Mononucleosis (Lumleian Lecture), *Lancet* **2** 180, 1934. (b) Baldrige, C. W., Rohner, F. J., and Hansmann, G. H. Glandular Fever (Infectious Mononucleosis), *Arch Int Med* **38** 413 (Oct.) 1926. (c) Sprunt, T. P. Infectious Mononucleosis (Glandular Fever), *Internat Clin* **3** 92, 1933. (d) McKinlay, C. A. Infectious Mononucleosis. I. Clinical Aspects, *J A M A* **105** 761 (Sept 7) 1935. (e) Nyfeldt, A. Etologie de la mononucléose infectieuse, *Compt rend Soc de biol* **101** 590, 1929. (f) Gorham, L. W., Smith, D. T., and Hunt, H. D. The Experimental Reproduction of the Blood Picture of Infectious Mononucleosis in the Guinea Pig, *J Clin Investigation* **7** 504, 1929.

<sup>277</sup> (a) Stuart, C. A., Burgess, A. M., Lawson, H. A., and Wellman, H. E. Some Cytologic and Serologic Aspects of Infectious Mononucleosis, *Arch Int Med* **54** 199 (Aug.) 1934. (b) Downey, H., and Stasney, J. Infectious Mononucleosis. II. Hematologic Studies, *J A M A* **105** 764 (Sept 7) 1935. (c) Baldrige <sup>276b</sup>. (d) Sprunt <sup>276c</sup>. (e) McKinlay <sup>276d</sup>.

Leukocytosis, <sup>278</sup> of varying degree, is present at some time during the course of the disease, leukopenia may occur at the onset. The usual white cell count is from 15,000 to 20,000 cells per cubic millimeter. The red blood cell count and the hemoglobin content are within normal limits. The exact classification of the atypical mononuclear cells observed is a difficult task. They have been accurately described by many authors. <sup>279</sup> It is generally accepted that they are of the lymphocytic series, though this view has many opponents.

Biopsy <sup>280</sup> of the glands involved reveals a rather characteristic picture. Grossly, the glands are of variable size, soft and spongy, with a distended white capsule. The normal architecture is obliterated. The lymphoid tissue as well as the reticulum is hyperplastic. The sinuses are compressed. The irregularity of the hyperplasia of the reticulum and lymphoid tissue gives the gland a characteristic nodular and spotty appearance.

The prognosis is very good, though relapses and remissions are not uncommon. Apparently the disease is self-limited. The course may be protracted, and both glandular and hematopoietic changes may persist for many months.

The diagnosis can be made usually by the presence of the painful glands and the characteristic changes in the blood. Recently, Paul and Bunnell <sup>281</sup> devised a heterophilic antibody test which appears to be practically specific for infectious mononucleosis (serum sickness to be excluded). This work has been confirmed by many investigators, <sup>282</sup>

278 Baldrige <sup>276b</sup> McKinlay <sup>276d</sup> Downey and Stasney <sup>277b</sup>

279 Cady, L. D. The Diagnosis of Sporadic Infectious Mononucleosis (Glandular Fever), *Am J M Sc* **175** 527, 1928. Osgood, E. E. Fenestration of Nuclei of Lymphocytes. A New Diagnostic Sign in Infectious Mononucleosis, *Proc Soc Exper Biol & Med* **33** 218, 1935. Baldrige <sup>276b</sup> Stuart, Burgess, Lawson and Wellman <sup>277a</sup> Downey and Stasney <sup>277b</sup>

280 Baldrige <sup>276b</sup> Downey and Stasney <sup>277b</sup>

281 Paul, J. R., and Bunnell, W. W. The Presence of Heterophile Antibodies in Infectious Mononucleosis, *Am J M Sc* **183** 90, 1932.

282 (a) Bunnell, W. W. A Diagnostic Test for Infectious Mononucleosis, *Am J M Sc* **186** 346, 1933. (b) Bailey, G. H., and Raffel, S. Hemolytic Antibodies for Sheep and Ox Erythrocytes in Infectious Mononucleosis, *J Clin Investigation* **14** 228, 1935. (c) Boveri, R. Ueber das Vorkommen heterophiler Antikörper bei lymphoidzelliger Angina, *Klin Wchnschr* **12** 666, 1933. (d) Rosenthal, N., and Wenkebach, G. Die Bedeutung der heterophilen Antikörperreaktion für die Diagnose der infektiösen Mononukleose, *ibid* **12** 499, 1933. (e) Van Ravenswaay, A. C. The Heterophile Agglutination Test in the Diagnosis of Infectious Mononucleosis, *New England J Med* **211** 1001, 1934. (f) Davidsohn, I. Infectious Mononucleosis, *Am J Dis Child* **49** 1222 (May) 1935. (g) Bernstein, A. Antibody Responses in Infectious Mononucleosis, *J Clin Investigation* **13** 419, 1934. (h) Butt, E. M., and Foord, A. G. The Heterophile Antibody Reaction in the Diagnosis of Infectious Mononucleosis, *J Lab & Clin Med* **20** 538, 1935.

although there is considerable difference of opinion as to the nature of the antibodies <sup>283</sup> involved in the reaction

There is no specific treatment for this malady. Rest in bed, forcing of fluids and a high caloric diet are indicated

#### AGRANULOCYTIC ANGINA

The following important aspects of this disease have been emphasized during the past year: (1) the importance of various drugs, especially aminopyrine, from an etiologic standpoint, (2) a more careful study of the pathologic process in the bone marrow, (3) attempts to produce the disease experimentally and (4) the value of various types of treatment

*Etiology*—Kracke and Parker <sup>284</sup> have written the most comprehensive article on the etiology of agranulocytic anemia. Their article includes a most complete and satisfactory summary of the knowledge with an extensive bibliography of the subject. They emphasized the facts that the disease occurred rarely before 1922, that it appears more frequently in women of middle age, that it is uncommon in Negroes and that it has its greatest incidence in persons of a social status above the average. In addition, they stated that it occurs most frequently in persons of the medical group and in countries, such as Germany and the United States, which "have become flooded with various synthetic drugs." All of these statements may be interpreted as suggestive evidence that a drug, such as aminopyrine, may be an important factor in causation of the disease. These authors concluded that a great deal of evidence has been accumulated which indicates that the administration of aminopyrine alone or in combination with one of the barbiturates is responsible for the disease in a large number of patients.

Kracke and Parker <sup>284</sup> emphasized, correctly, that it is almost impossible to obtain an accurate history as to the ingestion of drugs after a patient is dead, regardless of all statements of the immediate family and the attending physician. They cited examples which illustrate how difficult it may be to secure a reliable history even from a living patient and concluded that a "negative drug history is often a worthless one." While it is not claimed that all patients with agranulocytic angina have taken

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<sup>283</sup> Stuart, C. A. Heterophile Antibodies in Infectious Mononucleosis, *Proc Soc Exper Biol & Med* **32** 861, 1935. Davidsohn, I., and Walker, P. H. The Nature of the Heterophilic Antibodies in Infectious Mononucleosis, *Am J Clin Path* **5** 455, 1935. Paul and Bunnell <sup>281</sup>. Bailey and Raffel <sup>282b</sup>.

<sup>284</sup> Kracke, R. R., and Parker, F. P. The Relationship of Drug Therapy to Agranulocytosis, *J A M A* **105** 960 (Sept 21) 1935, Correction, *ibid* **105** 1047 (Sept 28) 1935.

aminopyrine, the foregoing statements may explain why some patients with agranulocytic angina are reported as not having taken the drug

Gordon <sup>285</sup> is not in accord with the more prevalent view that aminopyrine is an important factor in the production of agranulocytic angina. After questioning 59 of his patients, he concluded that in only 1 case could any therapeutic agent have been related to the etiology of the disease. In his opinion a number of factors may be responsible for the disease, but he considered that its absolute etiology is still unknown.

Jackson <sup>286</sup> stated that aminopyrine has an important etiologic significance in some cases, but he expressed the opinion that conclusive evidence has not demonstrated that it is the sole or even the major cause of the disease. In urging that caution be used in accepting this drug as an important cause of the agranulocytic state, he stated, in regard to its etiologic relationship to the disease, that some patients recover even though the aminopyrine therapy is continued and that in other patients there is no evidence to indicate that the drug was taken prior to the attack. He has observed patients who took aminopyrine and became ill with the disease, but despite the fact that the drug was discontinued one or more relapses occurred. In other patients, in whom the attack was precipitated by aminopyrine, there has been no evidence that after recovery they continue to be sensitive to it. This is evident as increasing doses have not produced a significant change in the blood picture. It has been stated that the incidence of the disease is becoming less, and this has been attributed to the withdrawal of the drug from the market. Yet the evidence indicates that the sales of this preparation had actually increased in the six months prior to the time Jackson's article was written.

Squier and Madison <sup>287</sup> reiterated their opinion that aminopyrine is a "frequent" etiologic factor in the production of the disease, as indicated in their previous paper, in which it was reported that 19 of their 20 patients had taken the drug directly before the onset of the condition. They presented observations on 2 patients which showed the effect on the granulocytes of the peripheral blood of 10 grains (0.65 Gm) of amytal compound (amytal with aminopyrine), 5 grains (0.324 Gm) of aminopyrine alone and the application of a 10 per cent solution of the latter drug to the unbroken skin. A significant granulopenia developed following the administration of the foregoing drugs, but there was no important change in the white blood cell count when amytal alone was

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285 Gordon, W. H. Malignant Neutropenia. Its Etiology and Treatment, J. Michigan M. Soc. **34** 7, 1935.

286 Jackson, H., Jr. Agranulocytosis, Ann. Int. Med. **9** 26, 1935.

287 Squier, T. L., and Madison, F. W. Drug Hypersensitivity as Cause of Acute Primary Granulocytopenia, Wisconsin M. J. **34** 175, 1935.

given. They concluded that the cause of the disease is an allergic response to certain drugs rather than a heightened pharmacologic or physiologic response.

Kastlin<sup>288</sup> and also Jackson<sup>286</sup> have made observations which indicate that there must be a variability of susceptibility in "sensitive" persons if aminopyrine plays an important etiologic rôle in this disease. The former reported the case of a patient who had taken aminopyrine for years on account of insomnia. Marked granulopenia developed (800 white blood cells per cubic millimeter), but recovery followed despite the daily administration of amytal and aminopyrine and of an allylisonopropyl barbituric acid with aminopyrine. With a recurrence of the granulopenia these drugs were withheld. After a temporary recovery the disease again progressed and terminated fatally.

Limarzi and Murphy<sup>289</sup> reported the case of a young woman who had five recurring attacks of agranulocytosis over a period of about two and one-half years. She had taken from 15 to 20 grains (1 to 1.3 Gm.) of aminopyrine, with or without acetylsalicylic acid, each week for the last four years and yet showed no clinical evidence of agranulocytosis in the interim between the five attacks. Furthermore, during the last attack, at which time the leukocyte count fell to 1,700 per cubic millimeter, with 12 per cent polymorphonuclear neutrophils, a total of 370 grains (24 Gm.) of aminopyrine was given. Despite this, the blood returned to normal, and the patient made a complete recovery. From this report and the others cited here, it is strongly suggested that if the condition is due to a susceptibility or idiosyncrasy to aminopyrine the degree must vary widely.

Stephens and Lawrence<sup>290</sup> observed a patient with recurrent attacks of agranulocytosis which occurred in association with the menstrual periods. Cyclic recurrences were present for one year after subtotal hysterectomy and bilateral salpingo-oophorectomy were done. At the end of this time administration of all drugs except codeine was omitted, and no further attacks occurred in the remaining ten months during which the patient was observed. Prior to the time of omission of the drugs, the patient had taken an unknown amount of aminopyrine. It was probably a considerable amount, as the patient had frequent migraine headaches and dysmenorrhea, for which she took aminopyrine,

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288 Kastlin, G. J. Primary Granulocytopenia, *Pennsylvania M. J.* **38** 600, 1935.

289 Limarzi, L. R., and Murphy, I. G. Amidopyrine and Granulopenia. Reappearance of Granulocytosis in Cases of Recurring Agranulocytosis After Large Doses of Amidopyrine, *Clinical Experiment, J. Lab. & Clin. Med.* **20** 616, 1935.

290 Stephens, D. J., and Lawrence, J. S. Cyclical Agranulocytic Angina, *Ann. Int. Med.* **9** 31, 1935.



acetylsalicylic acid and sodium amytal. The authors were unable to state if the omission of the aminopyrine was responsible for the disappearance of the recurrences.

*Pathology of the Bone Marrow*—Custer,<sup>291</sup> after a study of 11 cases, concluded that the histopathologic picture of the bone marrow is fairly constant. He attributed the previous inconsistent reports to (1) failure to examine the marrow from more than one site in the body and to (2) faulty technic, which makes accurate cell identification impossible. According to him, the marrow shows a striking proliferative activity of the myeloblasts. This is in contrast to the marrow of a normal person, in which the predominating cells of the granulocyte series are promyelocytes and myelocytes. Myeloblasts are rarely present. Custer considered that there is a failure of the myeloblasts to mature and that this is due to a lack of intrinsic maturation factor or the action of an extrinsic chemical or bacterial toxin. This observer furthermore stated that there is a difference between the marrow of persons with idiopathic agranulocytosis and that of persons with arsenical or septic neutropenia, as in the latter conditions the granular forms of the neutrophil series predominate.

*Attempts to Produce the Disease Experimentally*—Despite various attempts, it cannot be said that it is possible to produce true agranulocytosis in animals. This is not surprising if it is agreed that the condition occurs only in certain persons who are susceptible. If this is true one would not expect the disease to develop after the administration of aminopyrine or another drug unless the animal had a spontaneous sensitivity to it, or unless this state could be artificially induced.

Stenn<sup>292</sup> reported that he was unable to produce the disease in guinea-pigs, rabbits or monkeys when aminopyrine was given orally, subcutaneously, intraperitoneally and intravenously. He also was unable to produce the disease when the drug was injected into animals in which an attempt had been made to sensitize them to it. There was no evidence that aminopyrine could produce the disease in animals under the following circumstances: (1) when there was severe anemia as a result of bleeding, (2) after the bone marrow had been previously injured by the administration of benzene in olive oil, (3) after the animals had been infected for one month with *Bacillus subtilis*, *Streptococcus viridans* and *Salmonella supestifei*, and (4) after a complete fast of five days.

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291 Custer, R. P. Studies on the Structure and Function of Bone Marrow. Bone Marrow in Agranulocytosis, *Am J M Sc* **189** 507, 1935.

292 Stenn, F. Etiologic Relationship of Amidopyrine to Agranulocytosis, *J Lab & Clin Med* **20** 1150, 1935.

Kunde and his co-workers<sup>293</sup> were unable to produce granulopenia when from 1 to 4 tablets of cibalgin (aminopyrine [dimethylamino-phenyl-di-methylpyrazolone] and dial [diallylmalonylurea]) were given to rabbits for seventeen consecutive days. These drugs failed to prevent the leukocytosis which occurs in rabbits with sniffles or a "certain gastrointestinal infection." Rabbits in which the thyroid gland had been removed six weeks previously were given cibalgin, and leukocytosis developed in response to the infection which was comparable to that which occurred in rabbits with intact thyroids.

Smith and Mack<sup>294</sup> gave 0.75 Gm each of amytal and aminopyrine to 60 day old rats which had been placed on the following deficient diet: commercial casein, 18 per cent, corn starch, 54 per cent, butter fat, 18 per cent, lard, 6 per cent, and the Osborne-Mendel salt mixture, 4 per cent. The white blood cell counts of the animals were reduced 50 per cent, although there was no significant reduction in the number of granulocytes. There was continuous hematuria after the experiment had been in progress for a few days. A control group of rats which received a deficient diet alone did not show a reduction in the white blood cell count.

Climenko<sup>295</sup> studied the inhibiting effect of aminopyrine, antipyrine, alpha-di-nitrophenol, phenylhydrazine hydrochloride, catechol and ortho-quinone on the leukocytosis which is ordinarily produced in the rabbit by the parenteral injection of nucleic acid. He reported detailed observations on 1 animal which were typical of the results on 7 others. The intramuscular injection of 5 mg of nucleic acid per kilogram of body weight produced a maximum white blood cell count of 15,100 in four hours, 34 per cent of the cells being polymorphonuclear neutrophils. After the animal received 0.2 Gm of aminopyrine orally for eighteen days, a similar dose of nucleic acid was given intramuscularly. No significant response was evoked in the white blood cell count. Similar inhibitions were produced following the administration of the other drugs previously mentioned.

Bolton<sup>296</sup> reported the effects of aminopyrine, barbital, aminopyrine and barbital, phenylhydrazine and benzene on the cellular elements of

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293 Kunde, M. M., Herwick, R. P., Learner, A., and Sternback, M. Non-Production of Granulocytopenia with an Amidopyrine Compound (Cibalgin) in Some Acute Infections, *Proc Soc Exper Biol & Med* **32** 1121, 1935.

294 Smith, E., and Mack, L. Effect of Deficient Diet, Amytal and Amidopyrine on Blood Picture of Albino Rat, *Proc Soc Exper Biol & Med* **32** 1623, 1935.

295 Climenko, D. R. Inhibition of Leukogenic Activity in the Rabbit by Certain Cyclic Compounds, *Proc Soc Exper Biol & Med* **32** 823, 1935.

296 Bolton, V. L. Laboratory Study of Amidopyrine, Barbital, Phenylhydrazine and Benzene in Relation to Agranulocytic Angina, *J Lab & Clin Med* **20** 1199, 1935.

blood of normal dogs Of the 6 animals which were observed, there was a moderate drop in the leukocyte count in only 1 animal which received aminopyrine and 1 which received benzene As there were no significant changes in the percentage of granulocytes, it cannot be said that a blood picture similar to that observed in agranulocytic angina had been produced The author suggested that possibly the granulopenia of agranulocytic angina is due to transformation products of certain drugs which may in susceptible subjects cause arrested maturation of the myeloid elements of the bone marrow

Zia and Forkner<sup>297</sup> noted that acute granulopenia occurred in 8 of the 71 patients with visceral leishmaniasis whom they observed This was more than an intensification of the already existing leukopenia, as the polymorphonuclear neutrophils either abruptly decreased or completely disappeared from the peripheral blood The condition developed in 6 of these patients when they were undergoing treatment with urea stibamine (carbamide salt of p-amino-phenyl stibonic acid containing antimony in the pentavalent form) or neostibosan (p-amino-phenylstibinate of di-ethylamine, containing antimony in the pentavalent form)

These preparations were given intravenously to determine their effect on the blood of normal rabbits Repeated injections of large amounts did not cause the picture of acute agranulocytic angina in the peripheral blood

Harris and Schattenberg<sup>298</sup> studied the effect on experimental animals of the subcutaneous, intraperitoneal and intracardiac injection of *B enteritidis*, *B Welchii* and *Str haemolyticus* and toxic products derived from these bacteria The toxic material was prepared from the exudate obtained from guinea-pigs with fatal peritonitis which was induced by these organisms and was then passed through a Berkefeld or Seitz-Wertz filter When this was injected parenterally into guinea-pigs, granulopenia was induced The authors concluded that there is some doubt as to whether this condition resembles a true reproduction of the human disease They concluded also that these experiments indicate that agranulocytic angina is due to varied causes

*Treatment of Agranulocytosis*—Nonspecific therapy, stimulating doses of roentgen rays, liver extract, adenine sulfate, pentnucleotide, blood transfusions and leukocytic cream have been used as therapeutic

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297 Zia, L S, and Forkner, C E Acute Agranulocytosis of Kala-Azar Negative Effect of Urea Stibamine and Neostibosan (Antimony Preparations) on Blood of Normal Rabbits, *Proc Soc Exper Biol & Med* **32** 536, 1934

298 Harris, W H, and Schattenberg, H J Experimental Studies in So-Called Agranulocytic Angina Effects of Toxic Products of Certain Bacteria Recovered from Stool and Blood of Human Being upon Leukocytes of Animals *J Lab & Clin Med* **20** 1053 1935

agents in this disease. Although the administration of pentnucleotide has been used more than the other forms of treatment, it cannot be said that there is a general agreement concerning its value. Jackson<sup>286</sup> suggested the following possible explanations of why some unfavorable results have been reported. Less than 40 cc daily, which is the recommended dose, has been given. Unfortunately this dose may cause such severe reactions in some patients that it cannot be tolerated. Complete absence of granulocytes in the peripheral blood is incompatible with life. Despite an adequate dosage, therefore, the patient may die before the beneficial result occurs. The diagnosis of agranulocytosis may be incorrect, and the patient have some other disease such as leukemia.

According to Jackson,<sup>286</sup> if the patient has agranulocytosis anemia should not be present unless it is due to some unrelated disease, nor should there be thrombopenia, purpura or notable enlargement of the spleen, immature white blood cells should be absent from the peripheral blood, and there should be no lymphadenopathy except that which is due to the adjacent sepsis. He expressed the opinion that at present a larger number of patients have recovered after therapy with pentnucleotide than have survived after any other form of treatment. Injections of sterile milk, the use of leukocytic cream and roentgen therapy were considered useless. He is "decidedly" against transfusions of blood because there is no convincing evidence that they are beneficial, and in some instances the white blood cell count may fall following them. He stated that a few patients have been successfully treated with liver extract but that at present its ultimate value cannot be estimated.

He condemned sepsis as a therapeutic agent as there is no evidence that it can stimulate a paralyzed bone marrow.

He stated that the most effective therapy for the disease at present is as follows: (1) intelligent nursing care, (2) adequate fluids and food, (3) careful avoidance of sepsis, (4) administration of full doses of pentnucleotide, (5) the fearless use of such surgical measures as would be instituted in a person with a normal blood and (6) the use of codeine as a sedative.

Several observers have stated that pentnucleotide is the most hopeful remedy for the disease, although their results are not conclusive as the number of patients treated was small in each instance.<sup>299</sup>

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<sup>299</sup> Castleden, L. I. M. Agranulocytic Angina. Fatal Case Treated with Pentnucleotide, *Lancet* **1** 206, 1935. Fettes, J., and Whitby, L. E. H. Agranulocytic Angina. Failure with Pentnucleotide, *ibid* **1** 205, 1935. Morris, R. A., Miller, S., and Thacker Neville, W. S. Agranulocytic Angina, *Brit M J* **1** 1170, 1935. Hall, D. Agranulocytic Angina. Four Cases Treated with Pentnucleotide, *Lancet* **2** 1441, 1934. Smith, G. S. Case of Agranulocytosis Treated with Pentnucleotide, *ibid* **1** 607, 1935. Ranson, F. T. Case of Agranulocytic Angina *ibid* **1** 609, 1935.

Kracke and Parker<sup>284</sup> expressed the belief that the most valuable therapeutic measure is to refrain carefully from the use of drugs containing aminopyrine during the patient's illness. Minot and Castle<sup>300</sup> stated that the effectiveness of various therapeutic agents is difficult to estimate and that at present there is only general agreement that the patients should not be given aminopyrine during their illness.

### HEMATOLOGIC TECHNIC

Of basic importance in the study of the morphology of the blood, the evaluation of therapeutic measures and the analysis of statistical data are accepted standards for normal values. Such standards, based on the careful hematologic study of 500 rigidly selected healthy persons, have been compiled by Osgood<sup>301</sup>. They comprise values for the erythrocyte count, hemoglobin content, hemoglobin coefficient, color, volume and saturation indexes, reticulocyte count, total and differential leukocyte counts and sedimentation rate. Persons of both sexes and of all ages from 4 to over 30 years are represented.

Schnabel<sup>302</sup> and others have reemphasized the value of estimation of the size of the erythrocytes and the hemoglobin content as a means of classifying anemia on an etiologic as well as on a morphologic basis. The study, in conjunction, of the number, size and hemoglobin content of the red blood cells yields an insight into the nature of anemia caused by deficiency and provides a rational basis for its treatment.<sup>64</sup>

Although it is generally held that determination of the iron content of the whole blood yields no more information than an accurate estimation of the hemoglobin content, Josephs,<sup>303</sup> studying the blood of infants, found, especially between the second and the third week of life, that the hemoglobin value calculated from the iron content is appreciably higher than that obtained by the Newcomer method. He had no explanation for this discrepancy.

There is still lacking a standardized technic for the enumeration of the platelets. Two new modifications of older procedures have been proposed during the past year. One, described by Lempert,<sup>304</sup> is essentially

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300 Minot, George R, and Castle, W B. Malignant Neutropenia, in *The 1935 Year Book of General Medicine*, Chicago, Year Book Publishers, Inc., 1935, p 424.

301 Osgood, E E. Normal Hematologic Standards, *Arch Int Med* **56** 849 (Nov.) 1935.

302 Schnabel, T G. The Laboratory as an Approach to Anemic Therapy, *J Lab & Clin Med* **20** 714, 1935.

303 Josephs, H W. The Iron of the Blood. A Comparison of Values for Hemoglobin Determined by the Newcomer Method and Calculated from the Iron Content, *Bull Johns Hopkins Hosp* **56** 50, 1935.

304 Lempert, H. A Modified Technique for the Enumeration of Blood Platelets, *Lancet* **1** 151, 1935.

a simplification of Kristenson's direct method and employs a white blood cell pipet and a new diluting and hemolyzing fluid. The other, a modification of Fomic's indirect method, has been described by Gradwohl.<sup>305</sup> By staining for thirty minutes with diluted Giemsa stain, washing in neutral distilled water and restaining for thirty minutes, he has eliminated precipitate and obtained a deeper stain of the blood platelets. It is of interest that by these two radically different procedures the same range of normal values is obtained, from 250,000 to 350,000 platelets per cubic millimeter.

There is likewise a lack of a standardized procedure for the determination of the sedimentation rate or suspension stability of the erythrocytes. Although it has been contended that the use of potassium oxalate as an anticoagulant delays the rate of sedimentation as compared to the values obtained when heparinized blood is used, Wintrobe and Landsberg<sup>306</sup> have shown that this is not necessarily the case. By the use of a dry mixture of 6 mg of ammonium oxalate and 4 mg of potassium oxalate for each 5 cc of venous blood they eliminated any effect on the sedimentation rate as compared to that of heparinized blood. With the description of the instrument and the method employed in their studies, these authors give a chart for the correction of the sedimentation rate when alterations are due to anemia and consequent reduction of the volume of packed red cells. Another group of investigators<sup>307</sup> have determined that the sedimentation rate is increased both by heparin and by other anticoagulants when used dry. They found most satisfactory the use of a 3 per cent solution of sodium citrate and from 0.5 to 4.5 cc of blood. In Europe, much more than in America, attention has been given to microsedimentation methods. Raponsky,<sup>308</sup> who has written extensively on this subject, summarized the disadvantages of the macro-methods employing venous blood, chief among which are the inconvenience, the effect of stasis and the necessity of transferring the blood from one receptacle to another with consequent likelihood of altering the suspension stability. The usual drawbacks to the micromethods, he stated, are the danger of partial clotting, hemolysis and the difficulty of obtaining a uniform mixture of the blood with the anticoagulant. He expressed the belief that his technic, utilizing a specially constructed

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305 Gradwohl, R. B. H. A New Method of Staining Blood Platelets, *J. A. M. A.* **105** 1030 (Sept. 28) 1935.

306 Wintrobe, M. M., and Landsberg, J. W. A Standardized Technique for the Blood Sedimentation Test, *Am. J. M. Sc.* **189** 102, 1935.

307 Greisheimer, E. M., Hodapp, A., and Goldsworthy, E. Effect of Anticoagulants on Sedimentation Rate, *Am. J. M. Sc.* **190** 775, 1935.

308 Raponsky, A. I. Contribution a l'etude de la sedimentation sanguine. Methodes de la sedimentation sanguine, *Paris med.* **2** 461, 1934, 129, 1935.

pipet, obviates these disadvantages Bartsch<sup>309</sup> advocated the micro-procedure of Langer and Schmid and found that his results with it agree well with those obtained by the Westergren method Heimann<sup>310</sup> found that although the sedimentation rates determined on capillary and venous blood do not agree, the relative alterations are the same whether micro-methods or macromethods are used

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309 Bartsch, H Die Blutsenkungsreaktion nach der Micromethode, Deutsches Tuberk -Bl 9 46, 1935

310 Heimann, F Die sechsmomentige Mikrosedimentierung der roten Blutkörperchen und ihre Anwendung in Gynakologie und Geburtshilfe, Monatschr f Geburtsh u Gynak 98 266, 1935

## Book Reviews

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**Agents of Disease and Host Resistance** By Frederick P. Gay and others  
Price, \$10 Pp 1,581, with illustrations Springfield, Ill Charles C Thomas,  
Publisher, 1935

This huge tome is an encyclopedic work dealing with disease from the standpoint of the causes and the part that the host plays in the disease. Realizing that this subject was too inclusive for one author, Gay has used a collaborating staff of nineteen specialists, most of whom are associated with the College of Physicians and Surgeons of Columbia University.

The book confines itself largely to principles rather than to practice and does not contain, except in rare instances, any details concerning the technic of the laboratory sciences with which it deals. An attempt has been made to have the book fall somewhere between the designation of a textbook, on the one hand, and detailed systems or monographs on the other. In this respect the work is a success, for it will give the reader all that is necessary in most instances, unless he is specifically interested in some small part of a chapter. The liberal bibliography at the end of each chapter refers to works which, for the most part, have been published within the last two decades. The book is divided into twelve parts containing sixty-five chapters. These divisions are the general aspects of the causation, the classification and nature of disease, inanimate disease agents and tolerance, living disease agents, particularly bacteria, their morphology and physiology, infection and epidemiology, resistance and immunity, pathogenic bacteria and the diseases produced by them, pathogenic spirochetes and spirochetoses, pathogenic fungi and fungus diseases, indeterminate pathogenic forms and the diseases produced by them, animal pathogens, diseases of obscure etiology, and the practical results in the diagnosis, prevention and cure of infectious diseases. Throughout the book extensive use is made of tables. Two particularly valuable sets are that dealing with the chronology of the discovery of pathogenic agents and that dealing with the bacteriologic and immunologic tests used in the diagnosis of infectious diseases, although there are a host of other tables perhaps equally interesting and valuable.

For the most part, the findings of investigators are reviewed without concluding comments, yet in some instances the author has seen fit to express a definite opinion. For example, one finds such statements as the following: "In short, the entire hypothesis of selective localization is unfounded." When such conclusions are reached they are based on a rather careful evaluation of the material which has gone before. With the present interest in medical mycology, one will welcome the clear and concise chapter on this subject, much of the material in it represents original work of the author.

As in most books compiled by a group of authors, one finds inconsistencies, for example, the genus "Endameba" (which is incorrect) is used in the chapter dealing with pathogenic protozoa, while "Entameba" (also incorrect) is used in the chapter on the general physiology of micro-organisms. The same failure to correlate sections is noted in the chapter on chemotherapy, carbon tetrachloride is indicated for the treatment of hookworm without any reference to hexylresorcinol, which in turn is indicated as excellent treatment in the section dealing with hookworm disease. Some sections do not compare favorably with others. The chapter on animal parasites could definitely be improved in many particulars, chiefly by the inclusion of material which is omitted. For example, there are no mention of *Plasmodium ovale*, no discussion of the use of arsenic in amebiasis and no mention of the extensive monograph by Birkeland dealing with *Diphyllobothrium*, which, had it been examined, would have saved the author from the common error of indicating that fatal anemia is frequent in this type of infestation. One cannot help but wonder about the statement concerning the diagnosis of



trichiniasis, which recommends examination of the diaphragm in the region of the central tendon for larvae in the third week or later, if a diagnosis has not been established. This would be a drastic method, to say the least, in the average live human being! In the chapter dealing with chemotherapy there is no discussion of the treatment of amebiasis, although some experimental work is briefly mentioned. Another example of omission is the failure to discuss Kahn's recent work on the skin as a defensive mechanism. Since the book is well illustrated with many cuts and has many excellent color plates, it is curious that a figure so unrevealing as figure 140 should have found its way into the text.

In a work of this nature the index is, of course, important. In this work the index, which embraces nineteen pages, is well arranged, although there is some difficulty occasionally in finding titles, which should be expected. It would have been particularly advantageous to have appended an author's index.

In a book of this magnitude it is surprising that one can find so few complaints to register. That in itself should indicate that this work represents a distinct contribution to medical literature and that it will serve more or less as an encyclopedia for years to come.

**Bee Venom Therapy, Bee Venom, Its Nature, and Its Effects on Arthritic and Rheumatoid Conditions.** By Bodog F. Beck, M.D. Cloth. Price, \$5. Pp. 238. New York: D. Appleton-Century Company, Inc., 1935.

For centuries folk-lore has continued the idea that various diseases, "rheumatism" in particular, can be cured by bee stings or by the use of bee venom. The idea has been the basis of a therapy that has been dropped and revived many times. It is Beck's belief that it has been discarded so often not because of its lack of value but because of the difficulties inherent in the use of actual bee stings. Recently (1928), bee venom has been made commercially available in ampules for ready use. Bee venom therapy has regained considerable popularity in Europe but remains practically untried in this country. The author purposes to give a detailed description of the present status of such therapy in its modern modification and to present the results obtained by foreign workers, in order that "apitherapy" may at last be taken out of the hands of the laity and placed on a scientific basis.

To this end Beck has given an extensive review of a hundred years of medical and popular literature on the healing properties of bee venom. Chapters concern the use of animal venom and of formic acid (which, the author states, is contained in the venom of ants but not in that of bees), the chemistry and the physiologic effects of bee venom and bee stings, conditions of decreased and increased sensitivity thereto and the use of apitherapy for various types of rheumatism and arthritis. It is stated that "arthritic and rheumatic subjects" possess an abnormal (pathologic) immunity to bee venom and that patients with tuberculosis, syphilis and gonorrhea are unusually sensitive thereto—a point of almost diagnostic significance.

The author accepts as practically proved the theory that "rheumatic conditions" are the result of impaired circulation. In such disorders the endings of sympathetic nerves are overstimulated and produce vasoconstriction, with anemia of the tissues, and anoxemia and suboxidation result. In time this causes the accumulation of waste products, particularly lactic acid, in articular and muscular tissues. Bee venom contains an endothelial toxin which dilates capillaries and causes their walls to become permeable to corpuscles. It exerts its beneficial influence by accelerating and intensifying circulation to tissues presumably starved for blood. It is claimed that the venom is especially successful in cases of myositis, myalgia, neuritis and early rheumatoid arthritis and that it is "almost specific for rheumatic fever and endocarditis." The results are "very good" in Bechterew's spondylitis and are also good in acute and chronic gout.

Chapters on the effects of bee stings and on the treatment should be of interest and of some practical value to general practitioners and bee-keepers. The sections on the use of bees and bee venom are, unfortunately, of more historical than scientific value, as but few of the reports are critically reviewed. Several major

deficiencies in the author's presentation are recognizable at once to any one with an intimate knowledge of the modern problem of the rheumatic diseases. From the author's continuous use of the vague terms "rheumatism and arthritis" "arthritis caused by endocrine imbalance", "chronic arthritis", "arthritis deformans," and "rheumatoid heart affections," it would appear that his experience with rheumatic diseases is largely *ex bibliotheca*. His bland acceptance of the neurogenic theory and the lactic acid hypothesis puts him out of step with the great majority of recognized authorities in this field and dates his ideas to a previous medical generation. However, the reader who peruses the book with an open mind becomes affected by Beck's general optimism, is tolerant of the inadequacies of the quoted material and is ready to hear at last some new clinching evidence in favor of bee venom therapy, which is based on the author's series of cases—one series studied scientifically with adequate controls. Here the author lets his readers down completely. Not a single case of the author's is presented in detail or even in abstract. No table of his own results is given, merely the review of the writings of others and a summary of the testimonials of laymen and bee-keepers are offered. What little information is given on a plan of dosage or on the technic of administration is incomplete and poorly defined. Beck's reason for omitting any enumeration of records of his own cases is that he is pressed for information on his technic of administration, and "in order not to delay publication any longer" he "reserves the privilege of publishing my records at a later date." He states that he is convinced that the inclusion of additional reports of cases would be more disturbing than helpful. If his own records are no more adequately presented than those that he has reviewed, one is inclined to agree that they would be more disturbing than helpful. One must conclude that the author has, by this grave omission, failed completely in his purpose, that the value of bee venom is still a part of folk-lore or unscientific medical ideology and that bee venom therapy still awaits its Jenner.

**Urethrography Detailed Consideration in 154 Males** By Folke Knutsson  
*Acta radiologica*, supplement XXVIII Pp 155, with 55 illustrations 1935

In this publication one hundred and fifty-four cases of conditions studied by means of urethrograms are analyzed and the results are correlated with the clinical operative and pathologic findings. The conditions include strictures, urinary fistulas, and prostatic disease, both inflammatory and obstructive. In some cases the urethra was studied after operation and, interestingly, the results of prostatectomy were demonstrated.

Knutsson used iodized oil almost exclusively as his contrast medium, chiefly because of its low degree of irritation. Using a special syringe and clamp arrangement, he injected the medium and filled the urethra while the plates were being exposed, in order to visualize the posterior part of the urethra. One plate was exposed after injection of the medium in order to make possible study of the reflex contraction of the prostatic part of the urethra. Urethrograms were taken in the anteroposterior, lateral and right and left oblique positions.

In this series there were four cases of urethrovascular reflux, which the author believes can be avoided if urethrography is not done in the presence of urethral bleeding or if it does not follow too closely after sounding or cystoscopy.

The illustrations in this publication are remarkable and instructive, and the author's interpretations are accurate. The work has definite scientific value and proves that in many instances urethrograms are of distinct clinical advantage.

In criticism, the reviewer would suggest that a single contrast medium to be used in all cases is not adequate. In many instances a highly viscous medium, such as iodized K-Y jelly, is advantageous, in others a watery solution is preferable to oil. Iodized oil has the disadvantage of floating on urine and does not always give an accurate outline of the surface of the prostate adjoining the bladder.

**Body Water The Exchange of Fluids in Man** By John P Peters  
Price, \$4 Pp 405 Springfield, Ill Charles C Thomas, Publisher, 1935

The subject of the exchange of fluids in man has developed so rapidly and to such proportions that a review of it by some one who can speak with authority is badly needed. Peters is qualified to undertake such a review by his many years of study, as well as by his own many contributions in this field. Expressing the opinion that the conception of vital activity should be banished beyond the horizon of the research worker, he emphasizes the significance of physicochemical forces in the control of fluid exchange.

The subject is developed in twelve chapters. It may be considered in three parts.

The first part deals with the distribution of fluids in the body. The physicochemical principles underlying the passage of water and solutes in and out of the different compartments of the organism are presented, with special attention to the conclusions of Starling and the modification of these by later investigators. Special attention is paid to the equilibrium between hydrostatic pressure and the osmotic pressure of proteins and salts and to the permeability of biologic membranes. In spite of the fact that so much research has been carried on, a great amount of it in his laboratory, Peters feels that this part of the subject will be lacking in accuracy until better means are found for making chemical determinations of tissues and interstitial fluids.

The second part deals with the exchange of fluid between the body and its environment as this is effected through the respiratory tract and the skin. The subject of water balance receives a full discussion.

The third part, although allied to the second, deals with the kidney and its important part in the metabolism of water. The work of Richards is presented in detail, and the theory and observations of Rehberg are reviewed. In addition, the function of the isolated kidney is considered in relationship to the body as a whole.

The book is highly recommended. It is one of the most complete presentations of the subject, if not the most complete. It is well written and is accompanied by a large and well selected bibliography which will be of inestimable value to those specially interested in the field.

**Disease and Destiny** By Ralph H Major, M D With a preface by Logan Clendening, M D Price, \$3.50 Pp 338, with 47 illustrations New York D Appleton-Century Company, Inc, 1936

Major, Professor of Medicine in the University of Kansas, already known for his adventures into the field of general literature through "The Doctor Explains," now offers a volume which will appeal to every one with an interest in romance. "Disease and Destiny," like Zinsser's "Rats, Lice and History," vividly portrays the part played by disease in shaping the course of human events. The author has traveled extensively, for many years his vacations have been spent in acquiring a personal acquaintance with the settings of the events that he describes, and his studies in the original literature in medicine, embodied recently in another book, "Classic Descriptions of Disease," fit him well for the present task. It probably was a congenial task. The result will provide many a pleasant hour for the reader.

The subjects of the various chapters in the book are as follows: the black death, the plague which brought to an end the Golden Age of Pericles, typhus, which decimated many armies, including Napoleon's in Russia, "the king's evil," or scrofula, smallpox, membranous croup, "the pestilence that walketh in Darkness," or malaria, "the disease of Lazarus," or leprosy, "yellowjack," or yellow fever, "the legacy of bleeding" (hemophilia), which contributed to the downfall of the Russian Empire, and "the worst plague of all," syphilis.

**La maladie de Skévos Zervos ou maladie des pêcheurs d'éponges nus**  
By Skevos G Zervos Pp 29 Paris J B Bailliere et fils, 1935

In 1903 Skevos Zervos reported his observations on a disease afflicting many of the sponge fishers of his native Calymnos. The present volume is an interesting compilation of his continued studies of a hitherto undescribed disease. The condition was first named the disease of the naked sponge fishers, but, since it has been observed in other persons, the author ingenuously explains, it is now called the *maladie de Skevos Zervos*. This malady is characterized by a localized lesion which suppurates and becomes gangrenous and is associated with chills, fever, erythema, anorexia and prostration. The mortality is almost nil, but the morbidity is said to be high. The etiologic agent appears to be a venom produced by an actinian, a variety of sea-anemone, which Skevos Zervos says is parasitic on sponges in certain waters. The author states that the venom, which is most virulent in August, is introduced by way of scratches in the victim's skin. That the actinian is virulent and that the virulence is well known to the Aegean islander is indicated by the custom of feeding these anemones to cats and dogs in order to poison them. The animals die of convulsions directly afterward. It appears that this malady is a disease sui generis, due to some secretory product of the sea-anemones of that region and probably related to the sting of the giant medusa, or man-of-war, which, however, is much more benign.

**Archiv und Atlas der normalen und pathologischen Anatomie in typischen Rontgenbildern. Die theoretischen Grundlagen und Moglichkeiten der rontgendiagnostischen Weichteiluntersuchung.** By Dr Adolf Zuppinge. Paper. Price, 16 marks, bound, 18 marks. Pp 99, with 46 illustrations. Leipzig Georg Thieme, 1935.

As the title indicates, this brochure is devoted to a discussion of the theoretical bases and potentialities of roentgen depiction of soft tissues. Essentially, then, it gives an exposition of principles rather than a specific description of practical technics. It deals with the physical, physiologic and geometric factors which enter into roentgenography of soft parts and thus suggests methods by which favoring elements can be fostered and hindering elements can be combated. The reader who is confident in his understanding of the German language and is familiar with mathematical, geometric and trigonometrical formulas will find the book worth while, but the roentgenologist who has forgotten his academic training or the technician who is looking for ready-made technics is likely to find it disappointing.

**Zweite Internationale Kropfkongferenz.** Edited by Dr Otto Stiner. Price, 25 marks. Pp 698, with 128 illustrations and many tables. Bern Hans Huber, 1935.

This volume contains a report of the proceedings of the Second International Goiter Conference held in Bern between Aug 10 and 12, 1933. Obviously the program was carefully considered. It was divided, like Gaul, into three parts: first, hyperthyroid states received consideration, then were reported newer points of view regarding the cause of endemic goiter, and finally malignant diseases of the thyroid were discussed. A large group of investigators interested in goiter foregathered, and the list of those who presented papers is truly international. As published the papers are in French, German, Italian and English, all are short and give in abstract form the various readers' views. One can skim through the volume and pick out here and there almost anything one may wish to know concerning thyroid disorders. On the whole, the book is a convenient reference work. Perhaps it is more important for the larger medical libraries than for individual physicians to own this volume, although any one interested in goiter problems may wish to refer to it and will be glad to know of its publication.

**Localized Rarefying Conditions of Bone** By E S J King Price, \$7 50  
Pp 400, with 70 illustrations Baltimore William Wood & Company, 1935

This monograph, as the preface states, comprises material submitted for the Jacksonian Prize of the Royal College of Surgeons in 1933 and entitled "The Pathology, Diagnosis and Treatment of Localized Rarefying Changes in Bone as Exemplified by Legg-Perthes' Disease, Osgood-Schlatter's Disease, Kummell's Disease and Related Conditions" The special material is preceded by eighty-four pages of general considerations—bone formation and physiology, pathology, roentgenology and so on The special sections give the most intricate details of the subject of osteochondritis, there being separate sections, each with an extensive bibliography, on each bone The whole work is intensive and scholarly, obviously of great importance to the specialist

**The A B C of the Endocrines** By Jennie Gregory, M S Price, \$3 Pp 126,  
with illustrations Baltimore Williams & Wilkins Company, 1935

By means of a series of ingenious diagrams and sketches the author attempts to present a resume of the present knowledge of endocrinology The general style of this publication is sufficiently like that of a Mother Goose book to evoke a smile at first, but one soon realizes that this is no laughing matter at all and that the author has presented a sound, scholarly and immensely useful book of reference However, it is unfortunate that many of the diagrams must be a little hypothetical, in view of the rapidly changing status of certain phases of the subject

**Ueber Erkrankungen des arteriellen Systems** By F Curtius, R Engel,  
H Marx, and R Siebeck Price, 3 50 marks Pp 102 Leipzig Georg  
Thieme, 1935

This volume contains a series of five lectures for general practitioners on the subject of arterial disease, especially hypertension The discussion is adequate, well written and thoroughly in accord with modern practice, but nothing that is particularly new is brought out

**Studien zur Pathogenese** By Viktor von Wieszacker Price, 3 50 marks  
Pp 89 Leipzig Georg Thieme, 1935

Brief articles on certain psychiatric angles of disease are given here, but the material is not discussed in any systematic manner

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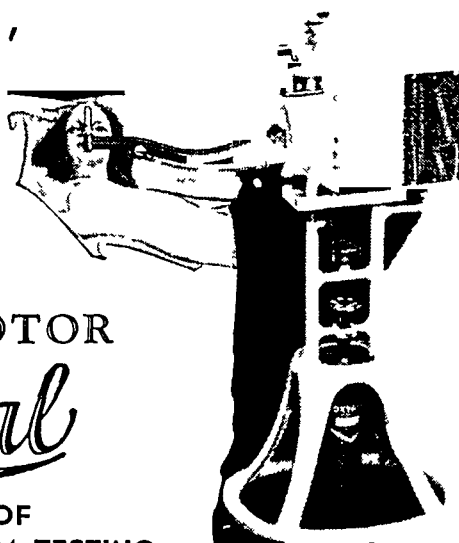
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